V. *Coronary Blood Flow Responses to Carbon Monoxide**

(a) INTRODUCTION

Coronary blood flow studies were designed to evaluate the response of this sectional circulation to various levels of carboxyhemoglobin. The major emphasis of these investigations was placed on the immediate response to an acute exposure when HbCO levels ranged from 5-40%. The actual mean HbCO levels attained were from 6.2 to 35.7%. A second group of animals were studied after they had been chronically exposed over a period of 6 weeks (4 hours daily) to an ambient environment containing 100 ppm of carbon monoxide. In another group animals had their conduction system (A-V node and Bundle of His) surgically removed to simulate a well known cardiac disorder. These animals have slowed heart rates and required the implantation of an external pacemaker in order to maintain adequate cardiovascular function. Animals from this group were studied at various intervals following the implantation of the externally charged pacemaker.

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* See pages 116-119 for literature references applicable to this section.

(b) GENERAL METHODS

Studies were performed on male mongrel dogs ranging in weight from 20 to 30 kg. All animals were maintained on a 12-hour light/dark cycle and were fasted for 16 hours prior to study. Experiments commenced at 8 a.m. with intravenous administration of sodium pentobarbital (25 mg/kg body weight). Light anesthesia, judged by preservation of corneal reflexes, was subsequently maintained by appropriate additional administration of pentobarbital.

A cuffed endotracheal tube was introduced and connected via a Collins "J" valve to an Instrument Associates ventilation meter, which was volumetrically calibrated prior to each experiment. Respiratory rate, tidal volume, and minute ventilation were recorded continuously. Expired gas volumes were expressed as STPD and BTPS. Expired gas samples were taken in 50-cc oiled glass syringes from a mixing chamber situated between the "J" valve and ventilation meter. Expired oxygen and carbon dioxide concentrations were ascertained by gas chromatography, checked by Haldane analysis. Respiratory ratio (R) and $\dot{V}_{O_2}$ were calculated for each sample period and standard formulas were used to calculate metabolic heat production.

Heparin (2.5 mg/kg) was administered intravenously and ECG limb leads were connected for continuous recording and direct writing as required (see later). Dacron catheters (7F) were advanced under fluoroscopy via carotid arteries and jugular veins to the right and left ventricles, coronary sinus, and pulmonary artery. A 50-cm polyethylene (PE 320) catheter was

advanced into the abdominal aorta via a femoral artery. Catheters were connected to Statham P23 BB and P23 Db transducers via multiple stopcock manifolds. Signal conditioning was performed by Honeywell (Accudata 113) strain-gauge bridge amplifiers and all pressures were recorded continuously, except during blood withdrawal, on a Honeywell 7600 14 channel magnetic tape recorder with reproduce circuit. Paper recordings of mean and pulsatile pressures and differentials were made at 15-min intervals at optimum amplifier gain on a Honeywell 1912 ultraviolet visicorder oscillograph with high and medium frequency galvanometers. Electronic differentiation was used to obtain peak positive and negative dp/dt's. The level of the right atrium was used as zero pressure reference, and prior to each photographic recording, transducers and amplifiers were zeroed and balanced with galvanometer outputs. Pressures and ECG were monitored on a multichannel oscilloscope. The following values were calculated: pulse pressure, mean stroke ejection rate, tension time index per beat and per minute, left ventricular stroke power, corrected ejection time, first differential index A and B, heart rate times arterial systolic pressure and diastolic pressure tension index.

The cardiac output was determined utilizing indocyanine green (Cardiogreen)*. Dye (0.5 mg) was injected into the right ventricle while sampling via a Gilford densitometer and Harvard withdrawal pump at a rate of 45.9 ml/min from the abdominal aorta. Dye curves were recorded with ECG on the visicorder and values

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* Supplied by Hynson, Westcott and Dunning, Inc. Pharmaceutical Laboratory, Baltimore, Maryland.

were instantaneously computed using a direct-reading Lexington cardiac output computer. The densitometer was calibrated before each experiment with a dye/blood dilution, the computer was adjusted to the known dye concentration and all gain outputs from dye and computer amplifiers were recorded. Reported values are the average of at least two technically adequate dye curves with less than five percent variation as determined by the cardiac output computer, and substantiated by periodic direct planimetry of the recorded curves. Cardiac output, heart rate and pressure values for each 15-min period were used to calculate: cardiac index, stroke volume, stroke index, total peripheral and pulmonary resistances, and left ventricular work, stroke work and stroke power.

Coronary blood flow was measured at 15-min intervals using I^{125} labeled antipyrine as the indicator (17, 25). After withdrawal of background samples from the left ventricle and coronary sinus, the indicator was infused into the right ventricle for 2 min and 15 sec with a Harvard infusion pump, while integrated arterial and coronary sinus samples were drawn during the last 2 min of infusion. The initial 15 sec of withdrawal was discarded to account for catheter dead space and right to left heart transit time. Sample activity was determined using a Nuclear Chicago automatic gamma counter, and the average activity of three 10-min determinations gave total counts in the range of 4000 after the first determination to 32,000 counts by the eighth determination. Previous results have demonstrated that coronary blood flow in dogs estimated by this method using iodinated antipyrine

is both accurate and precise (25). Standard formulas were used to calculate left ventricular mass, total left ventricular coronary blood flow per min and per 100 g/min, coronary resistance, and coronary blood flow as a percent of cardiac output.

Blood gas and biochemical samples were drawn in heparinized, oiled glass syringes concurrently with each coronary blood flow determination. Mercury was anaerobically introduced in each syringe to facilitate mixing and all samples were processed immediately. Blood gas syringes were stored at 4°C between duplicate analyses.

O_2 and CO_2 content of arterial, mixed venous, and coronary sinus blood was determined using an Infotronics (AD-200) blood gas chromatograph, which was calibrated prior to each experiment with precision tank gases (9). P_{O_2}, P_{CO_2}, and pH were determined using Radiometer microelectrodes and a Radiometer meter. The unit was calibrated hourly during analyses with precision tank gases and buffers. The following calculations were made for each sample period: arterial and coronary sinus O_2 saturation and total bicarbonate, total and left ventricular $M\dot{V}_{O_2}$, $M\dot{V}_{O_2}$ as a percent of whole body $\dot{V}_{O_2}$, left ventricular R, left ventricular efficiency and myocardial coefficient of oxygen extraction.

Hematocrit was done by microcapillary technique, hemoglobin by the cyanmethemoglobin method and plasma proteins by Goldberg refractometer. Lactate and glucose were determined by the Ström method (22), and the Hycel carbohydrate technique, respectively. Plasma non-esterified fatty acids were measured by the

colorimetric method (10). An Instrumentation Laboratories flame photometer was used for plasma Na^+ and K^+ determinations and Cl^- analysis was done by chloridometer. Osmolality was determined by the freezing point method using a Fisk osmometer. All instruments were calibrated daily. Myocardial A-V differences, left ventricular substrate utilization and extraction ratios were calculated for each period. Various procedures were utilized to provide a carbon monoxide load and are described in greater detail in appropriate sections.

A two-factor analysis of variance with repeated measures across both factors was utilized to examine the data. Where an omnibus F value was found to be significant, a post-hoc test of simple main effects was performed (24). If missing data was felt to preclude the analysis of variance, a paried Student *t*-test was used to test for differences between treatment correlations at each point in time. Regression equations (up to third order) were computed by the least squares method (24). All statistical procedures were performed on an IBM OS/360-75 computer.

(c) RESULTS AND DISCUSSION

(1) Normal Animals

The general methods described earlier were utilized in these studies. Carbon monoxide was given via a closed circuit rebreathing system of 5 liters containing a CO_2 scrubber of 250-ml volume. This method of CO administration permitted volumetric uptake of CO and greater control of final HbCO levels. Based on the animals' blood volume a selected volume of CO was added to the rebreathing system. The animals remained on the closed system for 2-3 minutes depending upon their ventilatory volume. Carbon monoxide was given in sufficient amounts to produce HbCO levels of approximately 0, 5, 10, 15, 20, and 35% HbCO 7.5 minutes after CO administration. After this step increment in CO, the animals were permitted to blow off the CO for the duration of the experiment. Statistical analysis of the data was performed using the Walsh Test (2).

a. Results: During the course of these studies carboxyhemoglobin levels were determined simultaneously in arterial and coronary sinus blood. The HbCO percentages were equivalent in these two areas regardless of the absolute concentrations of CO in the blood. The data obtained are summarized in Tables 10 and 11 and Figs. 10 to 15. Table 12 presents standard values for the various measurements made in these studies. The increase in coronary blood flow in the first minutes (7.5) following exposure to CO is shown in Fig. 10. Even at the lowest levels of carboxyhemoglobin (6.2%) flow increased approximately 20%. At the highest levels of HbCO (35.6%) flow had increased to slightly over 30%. Cardiac output remained constant

TABLE 10

SYSTEMIC CARDIORESPIRATORY RESPONSES TO AN ACUTE INHALATION OF CARBON MONOXIDE PRODUCING VARIOUS LEVELS OF CARBOXYHEMOGLOBIN

	Group I			Group II			Group III			Group IV			Group V		
	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P
n	10	10		13	13		8	8		7	7		7	7	
Weight (kg)	22.4			26.7			26.4			22.9			25.7		
BSA (m^2)	0.89			1.01			1.00			0.91			0.98		
%HbCO	0.5	6.2	0.005	0.5	10.3	0.008	0.6	14.0	0.031	0.6	22.9	0.008	0.6	35.6	0.008
Cardiac Index (liters/min/m^2)	3.54	3.55	NS	4.36	4.20	NS	3.82	3.87	NS	3.36	3.74	NS	4.19	4.20	NS
Heart Rate (beats/min)	132	139	0.025	138	159	0.016	128	149	0.062	125	152	0.008	137	162	0.008
Arterial Pressure, Systolic (torr)	172	172	NS	171	171	NS	173	174	NS	179	170	NS	185	176	NS
Arterial Pressure, Diastolic (torr)	121	120	NS	117	118	NS	117	114	NS	120	114	NS	127	121	NS
Peripheral Resistance (dynes·sec/cm5)	3333	3508	NS	2659	2787	NS	3091	2844	NS	3722	3272	0.055	3019	2871	NS
Left Ventricular Systolic Pressure (torr)	157	157	NS	160	162	NS	160	160	NS	164	159	NS	168	157	NS
Left Ventricular Mean Pressure (torr)	60	66	NS	67	78	NS	81	80	NS	68	66	NS	71	69	NS
Left Ventricular dp/dt (torr/sec)	3005	3428	NS	2845	3407	NS	2892	4088	NS	2250	2517	NS	3814	4029	NS
Right Ventricular Systolic Pressure (torr)	38.1	37.1	NS	40.0	39.9	NS	39.0	37.0	NS	34.3	34.7	NS	37.0	37.7	NS
Right Ventricular Mean Pressure (torr)	9.3	9.0	NS	8.3	11.1	NS	5.8	6.6	NS	7.3	8.6	NS	7.7	8.0	NS
Corrected Ejection Time (sec)	0.34	0.35	NS	0.36	0.38	NS	0.39	0.39	NS	0.28	0.31	NS	0.31	0.34	NS
Ventilation BTPS (liters/min)	4.85	5.87	NS	5.64	6.46	NS	5.12	6.50	0.031	4.90	5.76	0.008	6.43	7.76	0.008
Respiration Rate (breaths/min)	14	18	NS	10	18	0.023	15	26	0.031	17	22	0.016	16	26	0.016
O_2 Uptake (ml/kg)	5.63	5.98	NS	6.10	6.15	0.055	5.02	5.08	0.062	5.96	5.93	NS	6.17	6.86	NS
$\dot{R}$	0.92	0.87	NS	0.85	0.83	NS	0.91	0.88	NS	0.90	0.87	NS	0.87	0.78	NS
Rectal Temperature (°F)	100.4	100.5	NS	100.3	100.8	NS	101.0	101.1	NS	100.4	100.5	NS	101.0	101.3	NS

*7.5 min post CO inhalation.

TABLE 11

CORONARY BLOOD FLOW AND BLOOD GAS RESPONSES TO AN ACUTE INHALATION OF CARBON MONOXIDE PRODUCING VARIOUS LEVELS OF CARBOXYHEMOGLOBIN

	Group I			Group II			Group III			Group IV			Group V		
	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P
%HbCO	0.5	6.2	0.005	0.5	10.3	0.005	0.6	14.0	0.005	0.6	22.9	0.005	0.6	35.6	0.005
CBF (ml/min/100 g)	125	149	0.025	132	178	0.008	132	180	0.008	125	186	0.008	146	210	0.031
CBF/CO (%)	4.56	4.89	NS	3.42	5.78	0.008	5.14	6.37	0.031	4.45	5.80	0.016	4.37	6.27	0.031
CS Mean Pressure (torr)	1.43	1.03	NS	2.71	2.14	NS	1.66	2.02	NS	3.57	3.00	NS	2.02	2.85	NS
Left Ventricular Vascular Resistance (dynes·sec/cm^5)	806	740	0.056	828	645	0.008	678	570	0.062	846	578	0.008	722	506	0.031
Arterial O_2 Content (vol%)	17.46	16.65	0.005	17.25	16.23	0.008	17.86	16.41	0.031	18.07	14.72	0.008	17.15	12.11	0.008
CS O_2 Content (vol%)	4.86	4.73	0.056	4.45	4.88	0.016	4.89	5.31	0.031	4.71	5.67	0.016	4.25	5.32	0.016
Left Ventricular O_2 Uptake (ml/min/100 g)	17.1	17.6	0.056	15.6	19.6	0.055	20.5	22.2	0.062	16.9	16.9	NS	18.7	14.9	0.062
Left Ventricular Work (kg/min·m^2)	7.21	7.45	NS	9.21	9.12	NS	8.47	8.51	NS	7.05	7.82	NS	9.31	8.67	NS
Left Ventricular Efficiency (%)	21.7	20.5	NS	28.2	24.3	0.008	21.5	22.1	NS	20.1	22.7	NS	20.4	25.7	NS
HR x Systolic Pressure x 10^2	231	242	NS	243	269	0.023	221	261	0.062	226	263	0.055	274	287	NS
Total Hb Sat. (%), Arterial	89.9	85.6	0.005	89.5	83.0	0.008	90.9	81.1	0.031	94.0	75.1	0.008	92.5	62.5	0.008
Total Hb Sat. (%), Coronary Sinus	25.1	24.3	NS	23.9	26.2	0.055	24.5	26.3	0.062	24.5	29.1	0.008	22.9	27.8	0.016
P_aO_2 (torr)	79.8	78.2	0.056	80.3	77.9	0.055	77.6	76.0	0.031	83.3	80.6	0.055	81.9	73.1	0.016
P_aCO_2 (torr)	33.2	29.5	0.011	31.2	29.1	NS	31.6	27.2	0.031	33.6	31.1	NS	32.7	32.2	NS
pH_a	7.332	7.353	NS	7.343	7.345	NS	7.340	7.336	NS	7.344	7.357	NS	7.365	7.362	NS
$P_{cs}O_2$ (torr)	24.9	21.6	0.005	21.9	19.4	0.023	24.5	20.0	0.031	24.0	19.9	0.008	23.0	17.7	0.023
$P_{cs}CO_2$ (torr)	45.1	42.5	0.004	44.5	42.7	0.055	43.7	41.2	0.062	45.9	40.1	0.008	47.9	40.5	0.008
pH_{cs}	7.280	7.306	0.011	7.282	7.310	0.008	7.291	7.310	0.031	7.283	7.318	0.016	7.301	7.336	0.016

*7.5 min post CO inhalation.

FIGURE 10

Coronary Blood Flow (LV) Response to Various Levels of Carboxyhemoglobin, Control Blood Flow Levels Were 130 ml/100 g·min.

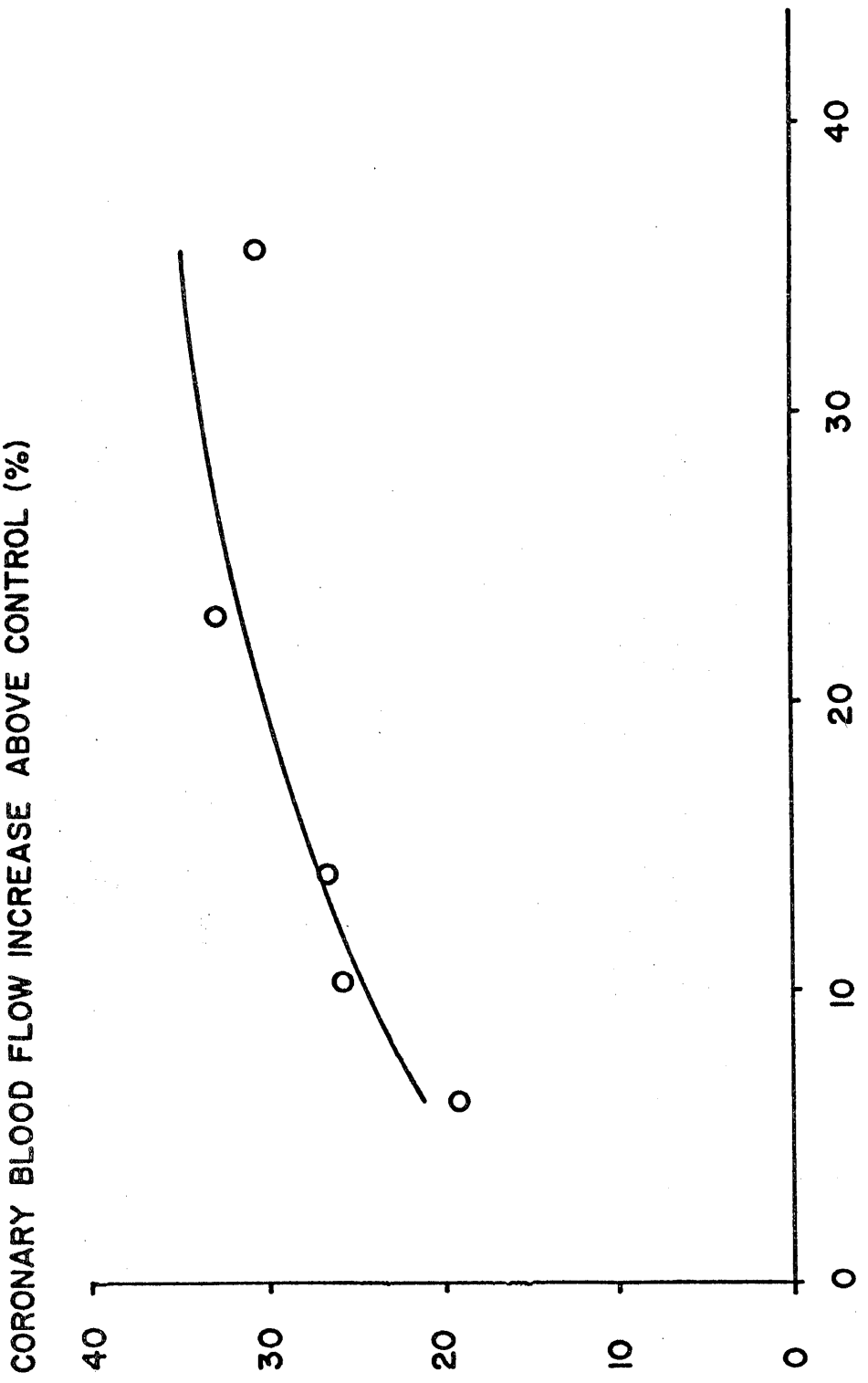


FIGURE 11

Alterations in Coronary Sinus P_{O_2} at Different Levels of Carboxyhemoglobin. The Regression Line Is Y = -0.0892X + 21.84, r = -0.496.

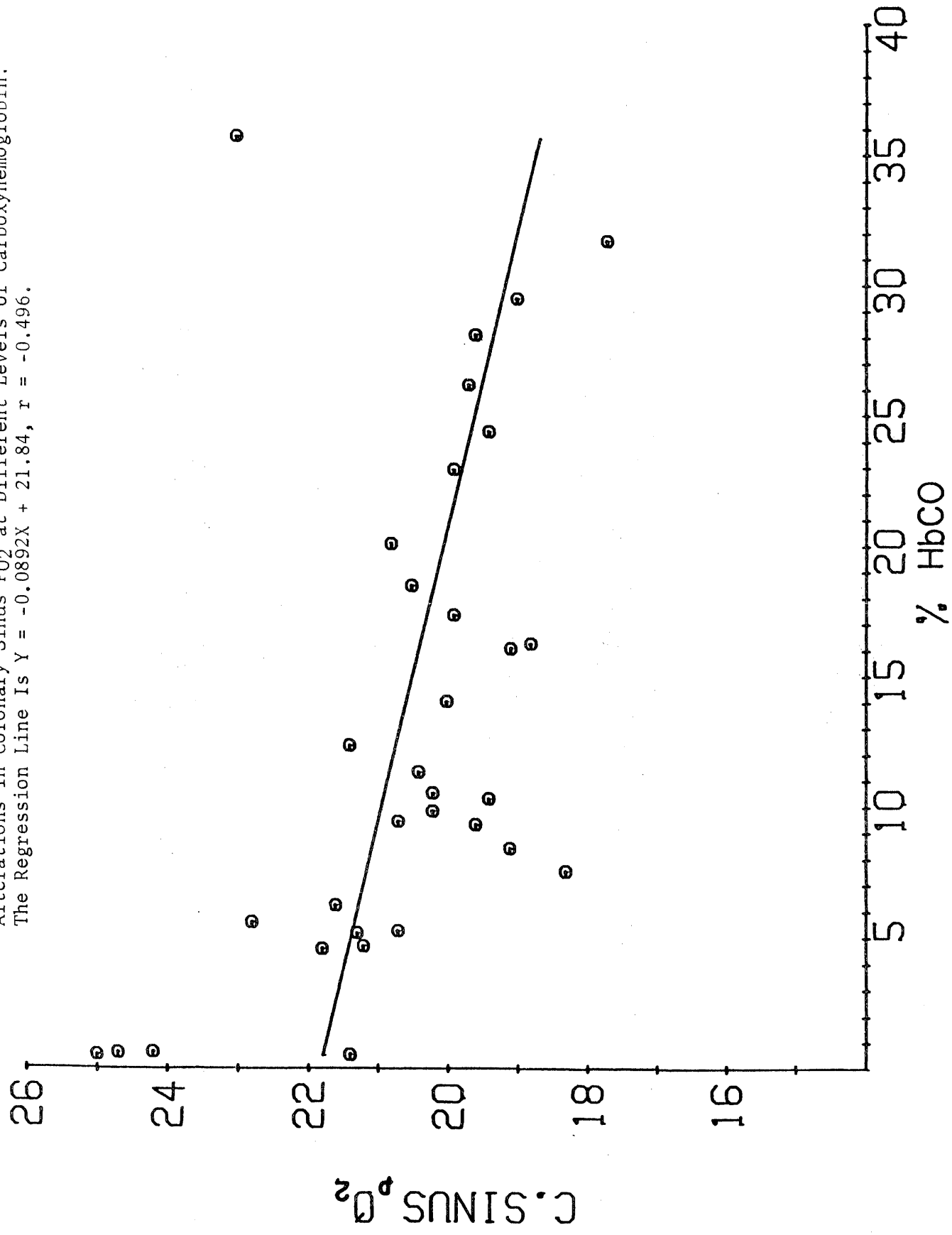


FIGURE 12

Decrease in the Oxygen Content of Arterial Blood at Various Levels of Carboxyhemoglobin. The Regression Line Is Y = 0.1312X - 0.4271, r = 0.974.

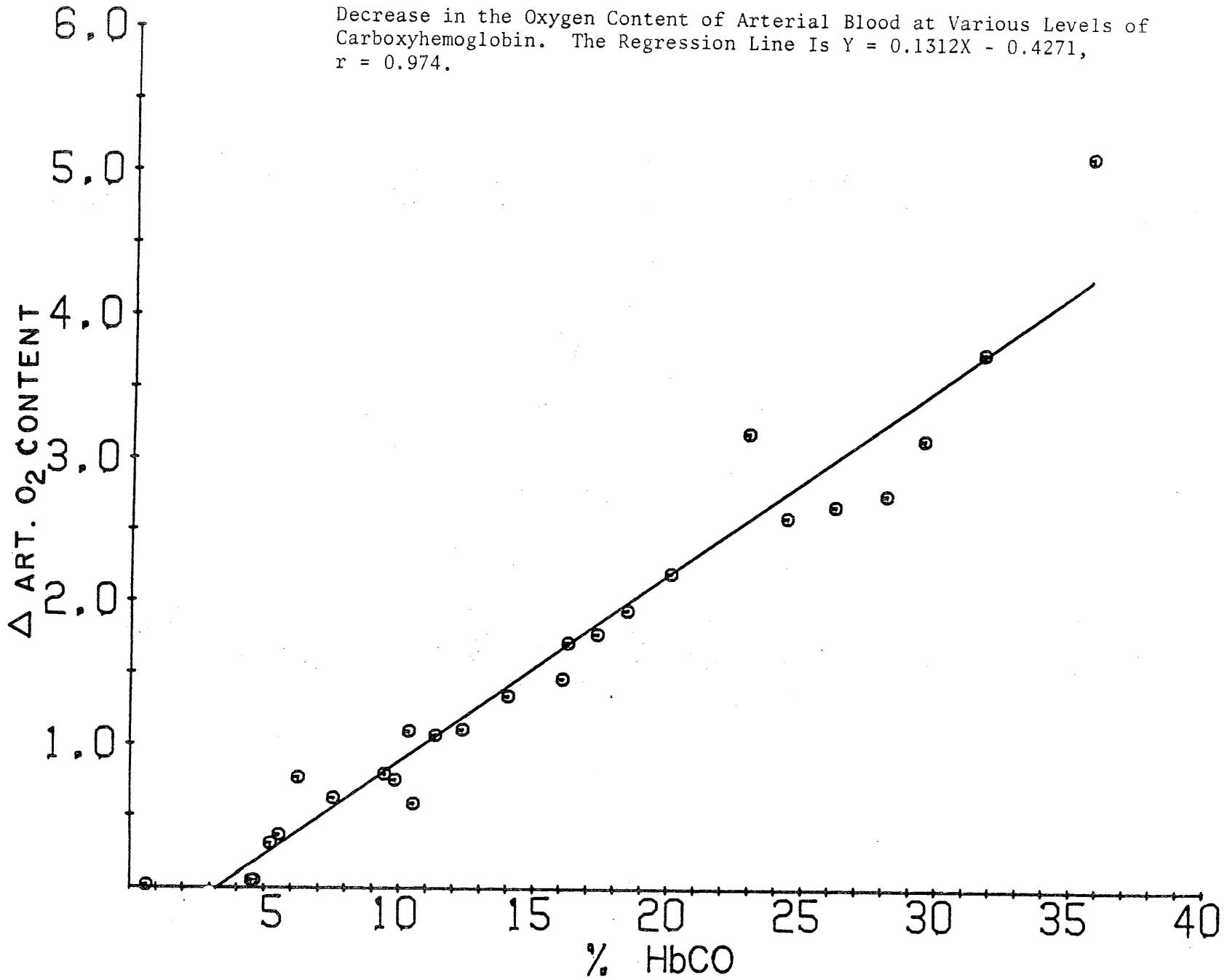


FIGURE 13

Oxygen Saturation (%) of Arterial Blood With Progressive Increases in the Level of Carboxyhemoglobin Present in the Arterial Blood. The Regression Line Is Y = -0.7023X + 91.740, r = -0.977.

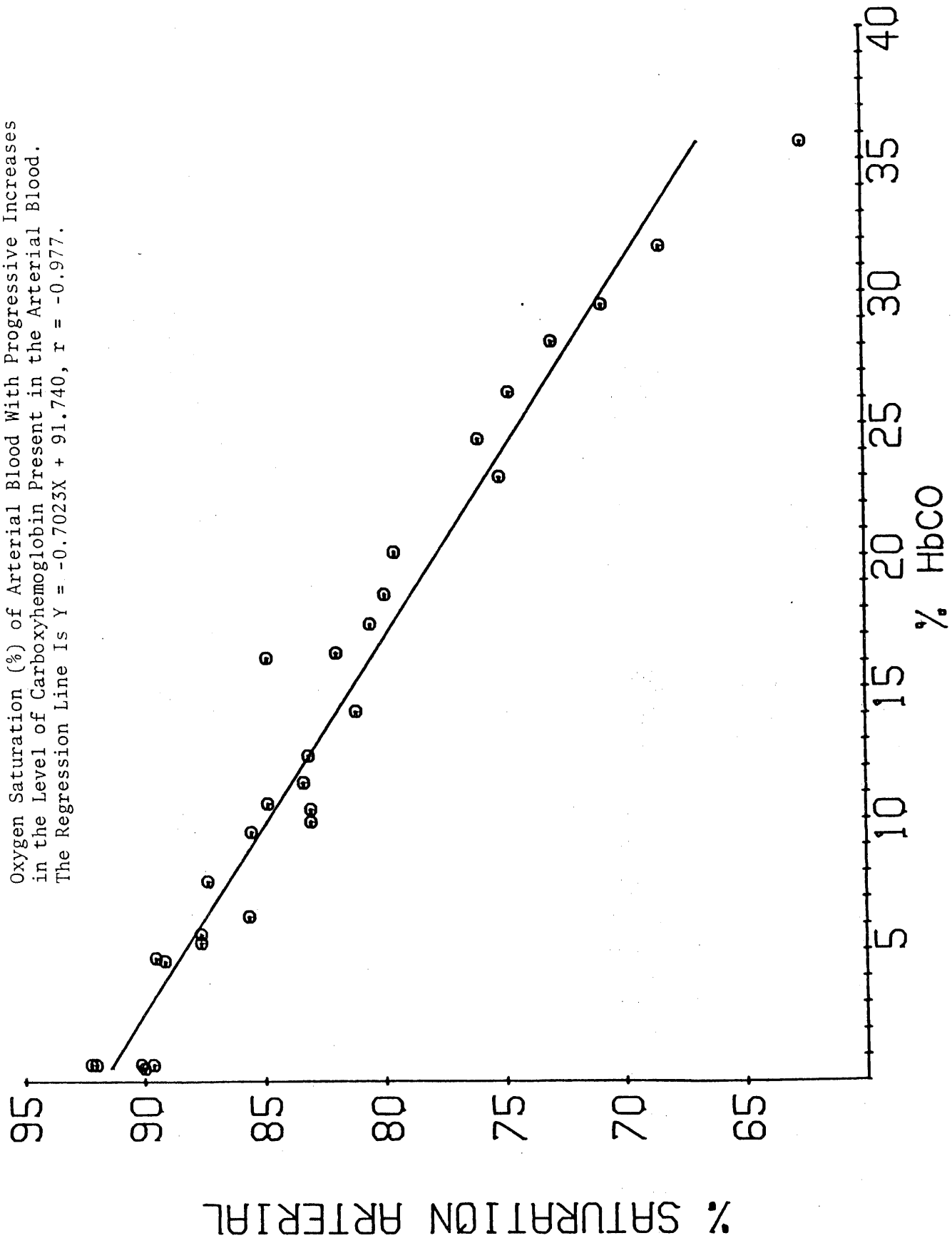
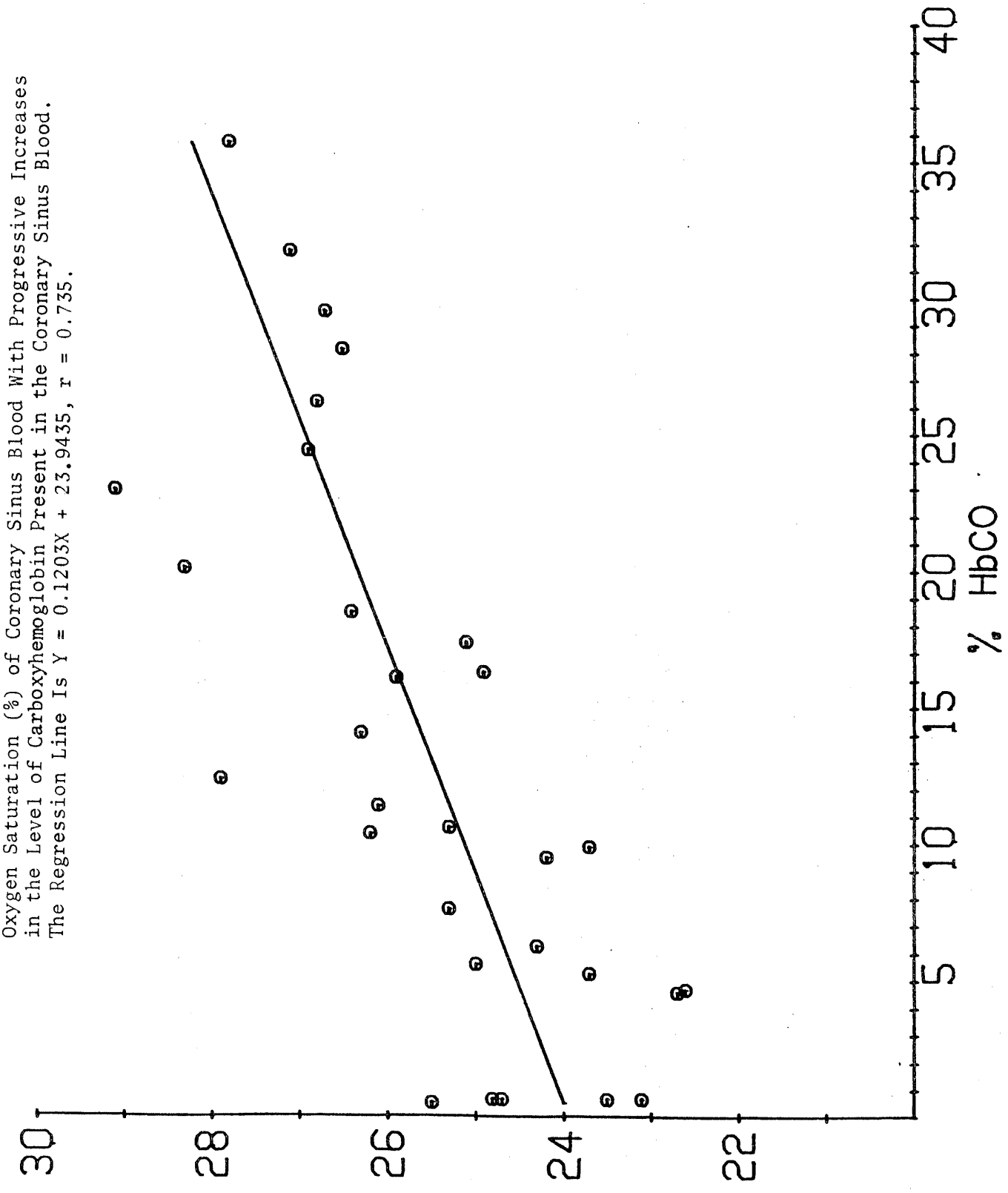


FIGURE 14

Oxygen Saturation (%) of Coronary Sinus Blood With Progressive Increases in the Level of Carboxyhemoglobin Present in the Coronary Sinus Blood. The Regression Line Is Y = 0.1203X + 23.9435, r = 0.735.



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(1) Normal Animals

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n	10	10		13	13		8	8		7	7		7	7	
Weight (kg)	22.4			26.7			26.4			22.9			25.7		
BSA (m^2)	0.89			1.01			1.00			0.91			0.98		
%HbCO	0.5	6.2	0.005	0.5	10.3	0.008	0.6	14.0	0.031	0.6	22.9	0.008	0.6	35.6	0.008
Cardiac Index (liters/min/m^2)	3.54	3.55	NS	4.36	4.20	NS	3.82	3.87	NS	3.36	3.74	NS	4.19	4.20	NS
Heart Rate (beats/min)	132	139	0.025	138	159	0.016	128	149	0.062	125	152	0.008	137	162	0.008
Arterial Pressure, Systolic (torr)	172	172	NS	171	171	NS	173	174	NS	179	170	NS	185	176	NS
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Peripheral Resistance (dynes·sec/cm^5)	3333	3508	NS	2659	2787	NS	3091	2844	NS	3722	3272	0.055	3019	2871	NS
Left Ventricular Systolic Pressure (torr)	157	157	NS	160	162	NS	160	160	NS	164	159	NS	168	157	NS
Left Ventricular Mean Pressure (torr)	60	66	NS	67	78	NS	81	80	NS	68	66	NS	71	69	NS
Left Ventricular dp/dt (torr/sec)	3005	3428	NS	2845	3407	NS	2892	4088	NS	2250	2517	NS	3814	4029	NS
Right Ventricular Systolic Pressure (torr)	38.1	37.1	NS	40.0	39.9	NS	39.0	37.0	NS	34.3	34.7	NS	37.0	37.7	NS
Right Ventricular Mean Pressure (torr)	9.3	9.0	NS	8.3	11.1	NS	5.8	6.6	NS	7.3	8.6	NS	7.7	8.0	NS
Corrected Ejection Time (sec)	0.34	0.35	NS	0.36	0.38	NS	0.39	0.39	NS	0.28	0.31	NS	0.31	0.34	NS
Ventilation BTPS (liters/min)	4.85	5.87	NS	5.64	6.46	NS	5.12	6.50	0.031	4.90	5.76	0.008	6.43	7.76	0.008
Respiration Rate (breaths/min)	14	18	NS	10	18	0.023	15	26	0.031	17	22	0.016	16	26	0.016
O_2 Uptake (ml/kg)	5.63	5.98	NS	6.10	6.15	0.055	5.02	5.08	0.062	5.96	5.93	NS	6.17	6.86	NS
$\dot{R}$	0.92	0.87	NS	0.85	0.83	NS	0.91	0.88	NS	0.90	0.87	NS	0.87	0.78	NS
Rectal Temperature (°F)	100.4	100.5	NS	100.3	100.8	NS	101.0	101.1	NS	100.4	100.5	NS	101.0	101.3	NS

*7.5 min post CO inhalation.

TABLE 11

CORONARY BLOOD FLOW AND BLOOD GAS RESPONSES TO AN ACUTE INHALATION OF CARBON MONOXIDE PRODUCING VARIOUS LEVELS OF CARBOXYHEMOGLOBIN

	Group I			Group II			Group III			Group IV			Group V		
	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P	Control	CO*	P
%HbCO	0.5	6.2	0.005	0.5	10.3	0.005	0.6	14.0	0.005	0.6	22.9	0.005	0.6	35.6	0.005
CBF (ml/min/100 g)	125	149	0.025	132	178	0.008	132	180	0.008	125	186	0.008	146	210	0.031
CBF/CO (%)	4.56	4.89	NS	3.42	5.78	0.008	5.14	6.37	0.031	4.45	5.80	0.016	4.37	6.27	0.031
CS Mean Pressure (torr)	1.43	1.03	NS	2.71	2.14	NS	1.66	2.02	NS	3.57	3.00	NS	2.02	2.85	NS
Left Ventricular Vascular Resistance (dynes·sec/cm^5)	806	740	0.056	828	645	0.008	678	570	0.062	846	578	0.008	722	506	0.031
Arterial O_2 Content (vol%)	17.46	16.65	0.005	17.25	16.23	0.008	17.86	16.41	0.031	18.07	14.72	0.008	17.15	12.11	0.008
CS O_2 Content (vol%)	4.86	4.73	0.056	4.45	4.88	0.016	4.89	5.31	0.031	4.71	5.67	0.016	4.25	5.32	0.016
Left Ventricular O_2 Uptake (ml/min/100 g)	17.1	17.6	0.056	15.6	19.6	0.055	20.5	22.2	0.062	16.9	16.9	NS	18.7	14.9	0.062
Left Ventricular Work (kg/min·m^2)	7.21	7.45	NS	9.21	9.12	NS	8.47	8.51	NS	7.05	7.82	NS	9.31	8.67	NS
Left Ventricular Efficiency (%)	21.7	20.5	NS	28.2	24.3	0.008	21.5	22.1	NS	20.1	22.7	NS	20.4	25.7	NS
HR x Systolic Pressure x 10^2	231	242	NS	243	269	0.023	221	261	0.062	226	263	0.055	274	287	NS
Total Hb Sat. (%), Arterial	89.9	85.6	0.005	89.5	83.0	0.008	90.9	81.1	0.031	94.0	75.1	0.008	92.5	62.5	0.008
Total Hb Sat. (%), Coronary Sinus	25.1	24.3	NS	23.9	26.2	0.055	24.5	26.3	0.062	24.5	29.1	0.008	22.9	27.8	0.016
P_aO_2 (torr)	79.8	78.2	0.056	80.3	77.9	0.055	77.6	76.0	0.031	83.3	80.6	0.055	81.9	73.1	0.016
P_aCO_2 (torr)	33.2	29.5	0.011	31.2	29.1	NS	31.6	27.2	0.031	33.6	31.1	NS	32.7	32.2	NS
pH_a	7.332	7.353	NS	7.343	7.345	NS	7.340	7.336	NS	7.344	7.357	NS	7.365	7.362	NS
$P_{cs}O_2$ (torr)	24.9	21.6	0.005	21.9	19.4	0.023	24.5	20.0	0.031	24.0	19.9	0.008	23.0	17.7	0.023
$P_{cs}CO_2$ (torr)	45.1	42.5	0.004	44.5	42.7	0.055	43.7	41.2	0.062	45.9	40.1	0.008	47.9	40.5	0.008
pH_{cs}	7.280	7.306	0.011	7.282	7.310	0.008	7.291	7.310	0.031	7.283	7.318	0.016	7.301	7.336	0.016

*7.5 min post CO inhalation.

FIGURE 10

Coronary Blood Flow (LV) Response to Various Levels of Carboxyhemoglobin. Control Blood Flow Levels Were 130 ml/100 g·min.

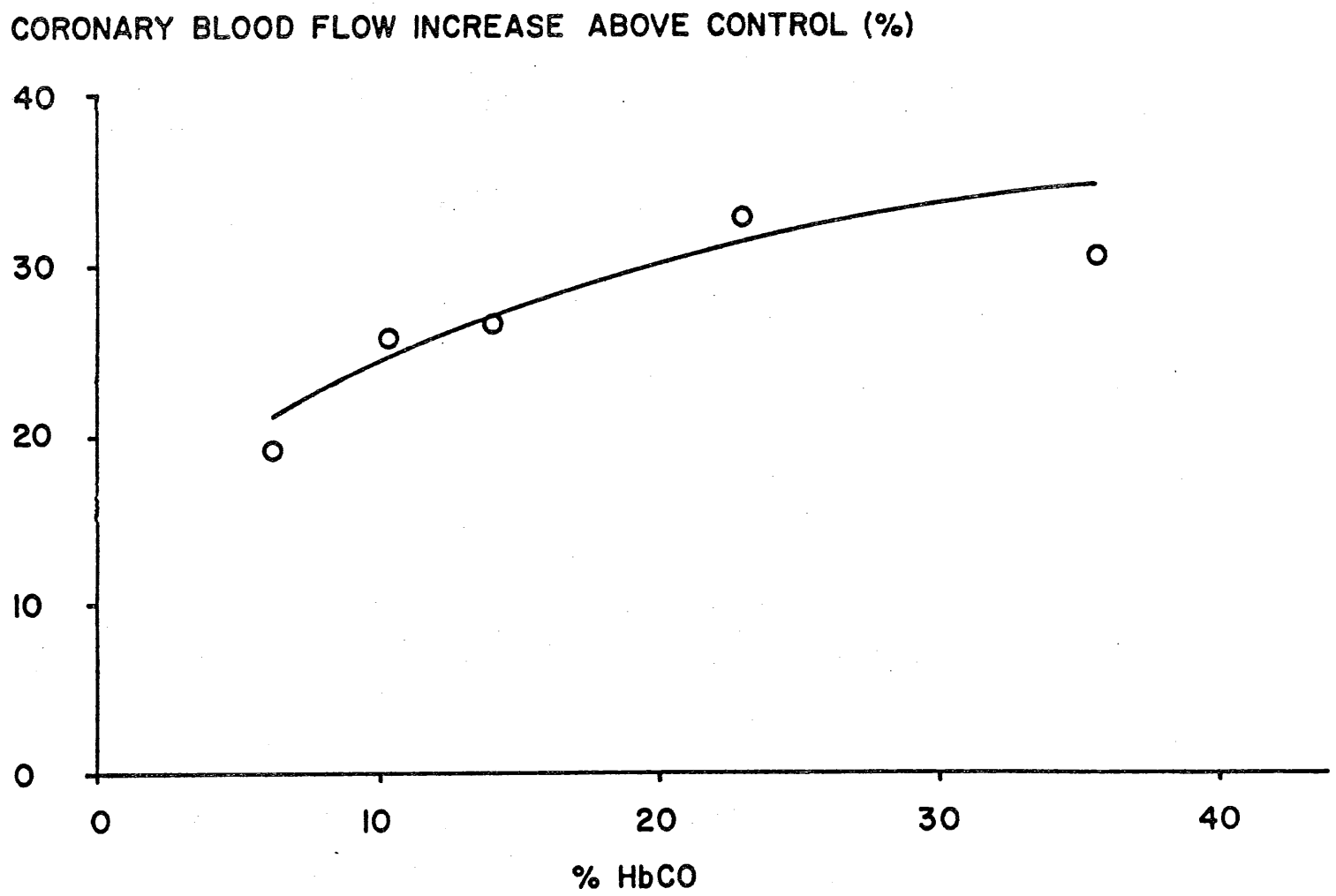

FIGURE 11

Alterations in Coronary Sinus P_{O_2} at Different Levels of Carboxyhemoglobin. The Regression Line Is Y = -0.0892X + 21.84, r = -0.496.

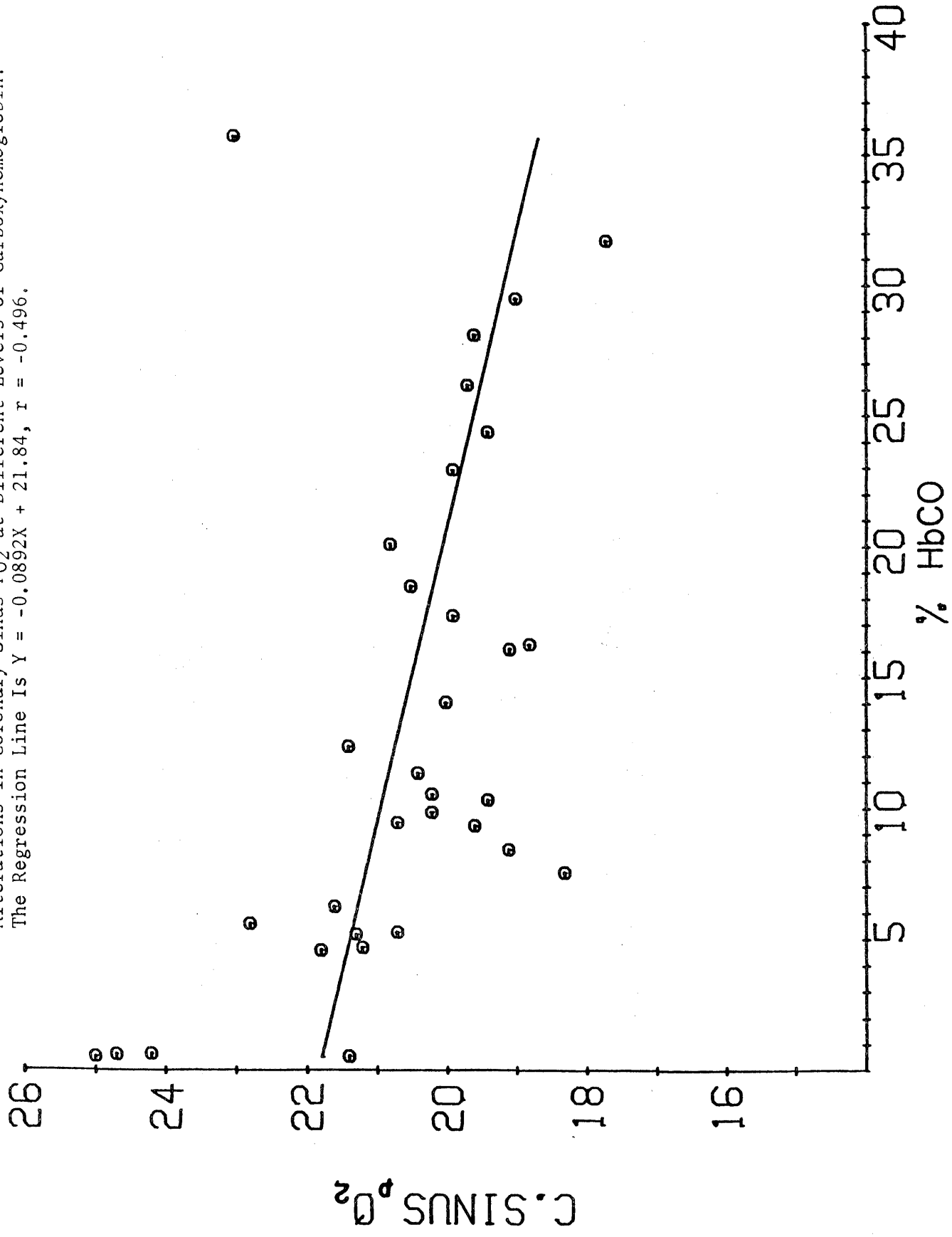

FIGURE 12

Decrease in the Oxygen Content of Arterial Blood at Various Levels of Carboxyhemoglobin. The Regression Line Is Y = 0.1312X - 0.4271, r = 0.974.

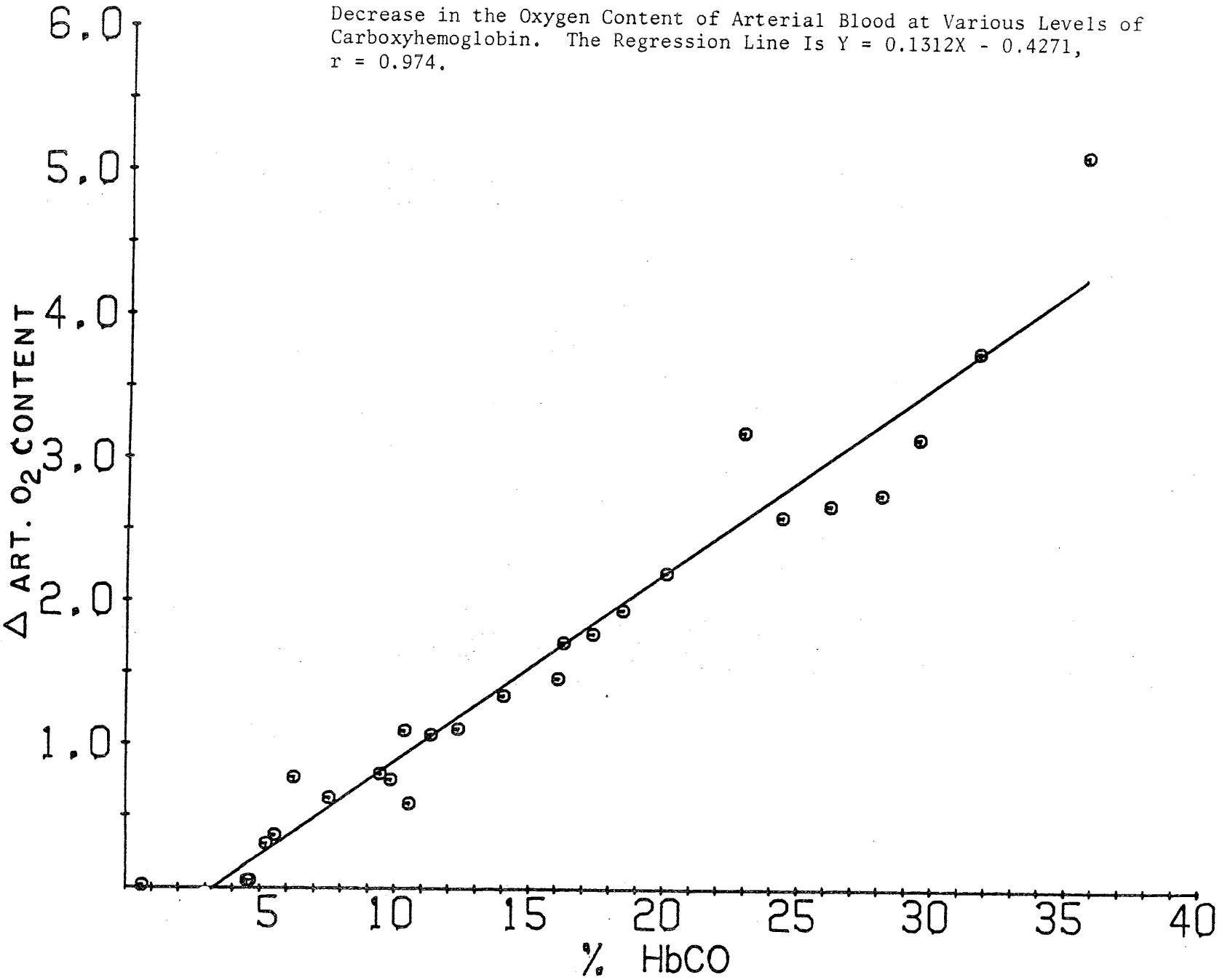

FIGURE 13

Oxygen Saturation (%) of Arterial Blood With Progressive Increases in the Level of Carboxyhemoglobin Present in the Arterial Blood. The Regression Line Is Y = -0.7023X + 91.740, r = -0.977.

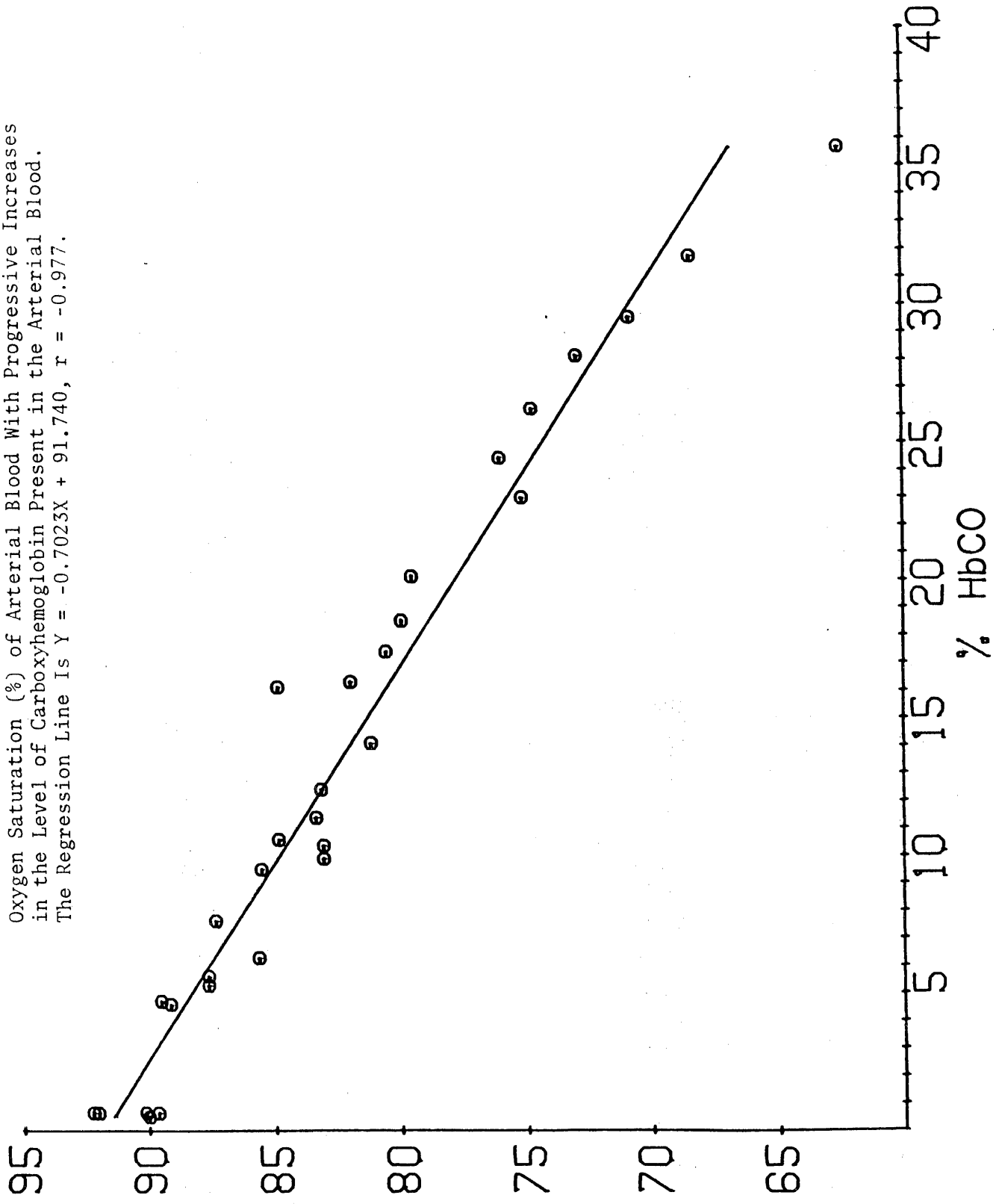

FIGURE 14

Oxygen Saturation (%) of Coronary Sinus Blood With Progressive Increases in the Level of Carboxyhemoglobin Present in the Coronary Sinus Blood. The Regression Line Is Y = 0.1203X + 23.9435, r = 0.735.

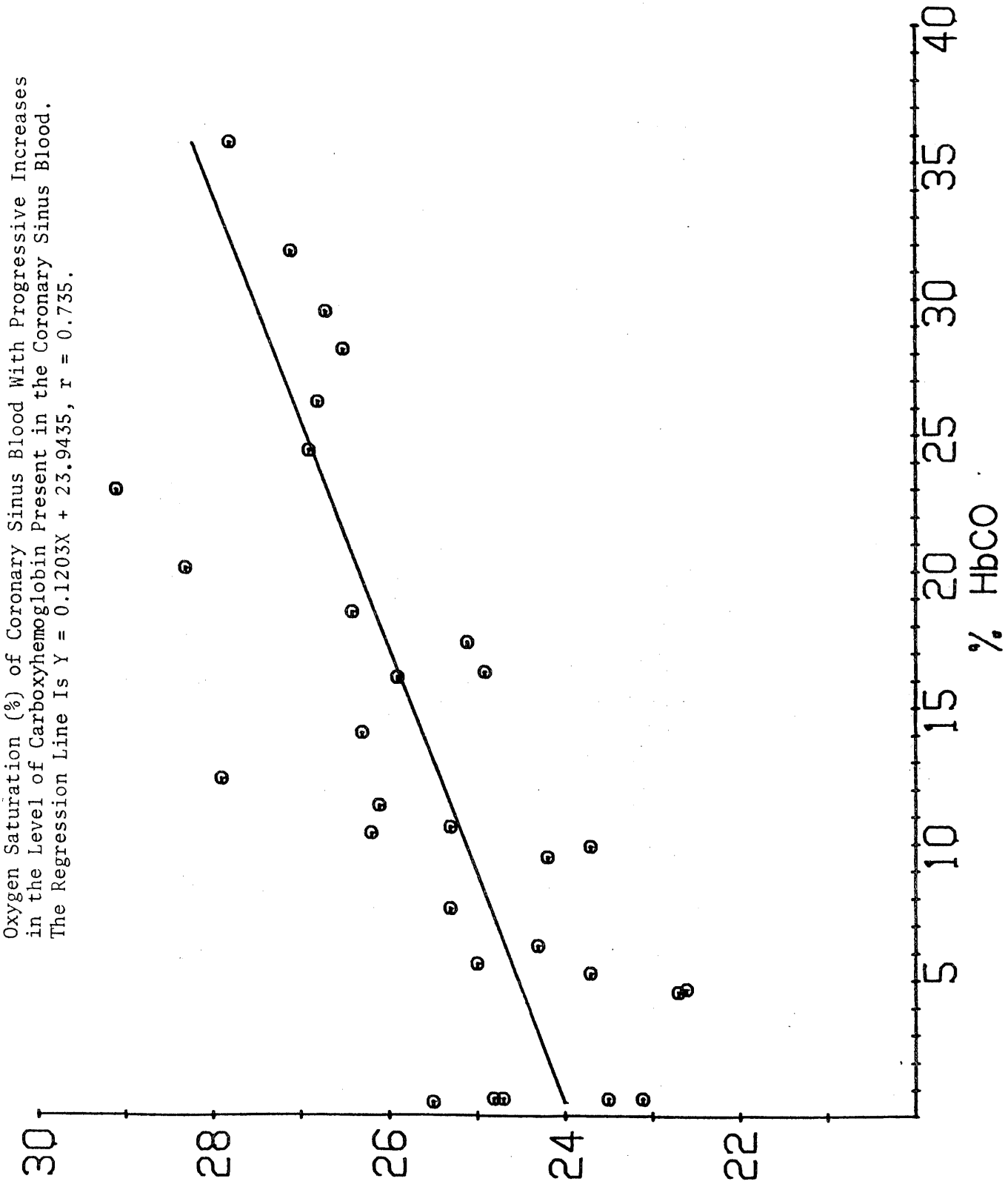

FIGURE 15

Ratio of Oxygen Content Differences (Arterial Minus Coronary Sinus) in Control (Ambient Air) and Carbon Monoxide Exposed Animals.
The Regression Line Is Y = 0.0159X + 1.1024, r = -0.948.

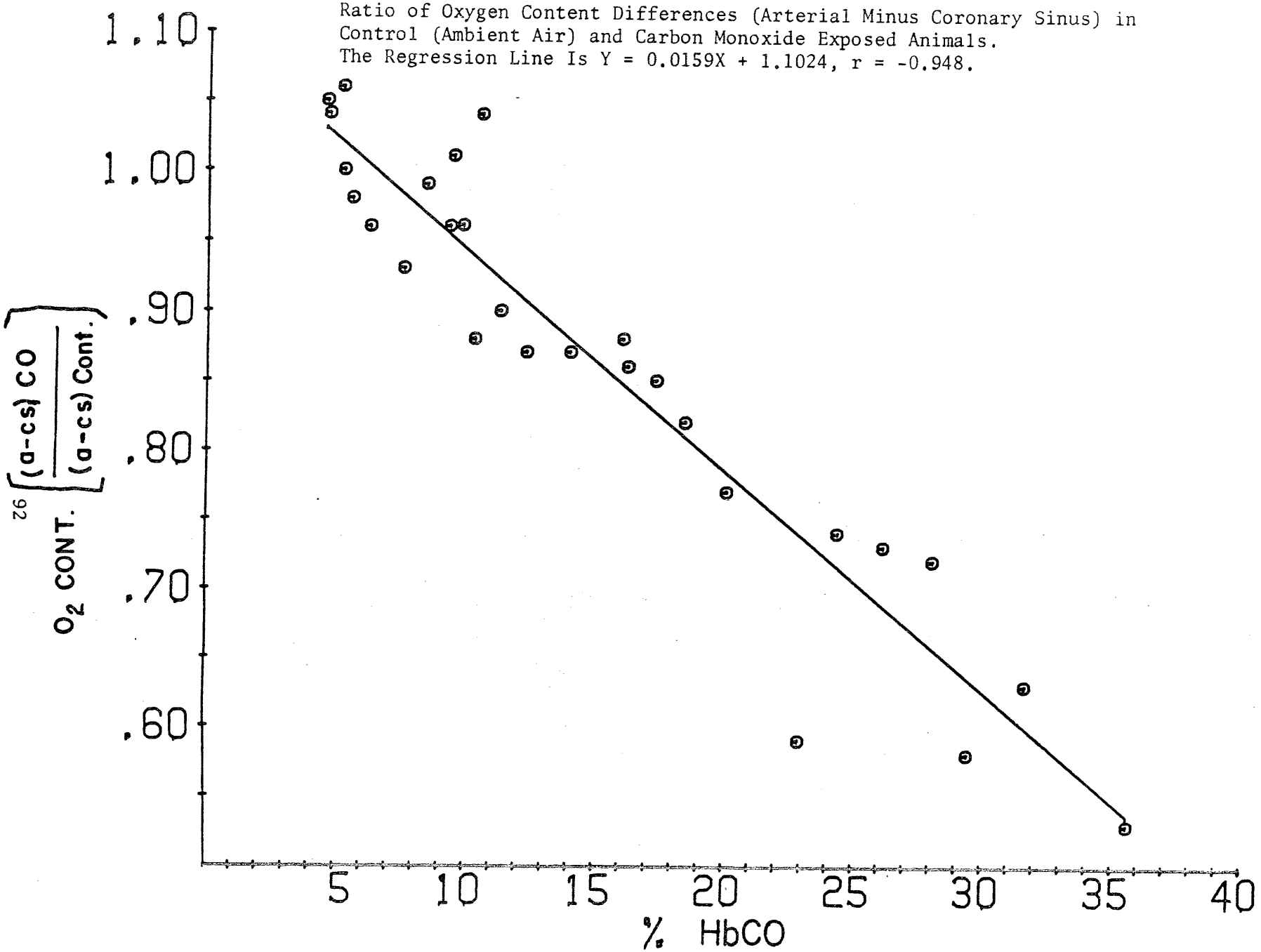

TABLE 12

CONTROL VALUES FOR VARIOUS CARDIORESPIRATORY MEASUREMENTS
(DUPLICATE VALUES AT 15-MIN INTERVALS IN 16 ANIMALS
WITH A MEAN WEIGHT OF 23.0 KG)

	Mean	±SE
Cardiac Index (liters/min·m^2)	3.95	0.22
Heart Rate (beats/min)	134	6.5
Stroke Index (ml/beat/m^2)	30	1.2
Arterial Pressure, Systolic (torr)	177	4.0
Arterial Pressure, Diastolic (torr)	120	3.0
Arterial Pressure, Mean (torr)	137	3.1
Peripheral Resistance (dynes·sec/cm^5)	2920	200
Left Ventricular Systolic Pressure (torr)	157.0	3.8
Left Ventricular Mean Pressure (torr)	66.0	2.8
Left Ventricular End Diastoles (torr)	9.2	1.0
Left Ventricular + dp/dt (torr/sec)	2901	276
Left Ventricular - dp/dt (torr/sec)	4181	273
Left Ventricular Work (kg·m/min/m^2)	8.0	0.6
Right Ventricular Systolic Pressure (torr)	35.2	2.9
Right Ventricular Mean Pressure (torr)	8.4	0.8
Right Ventricular End Diastoles (torr)	4.0	0.6
Right Ventricular + dp/dt (torr/sec)	844	124
Right Ventricular - dp/dt (torr/sec)	793	190
Systolic Ejection Period (sec)	0.213	0.010
Mean Systolic Ejection Rate (ml/m^2/sec)	147	10.0
Tension Time Index/Beat (torr·sec/beat)	34	1.9
Tension Time Index/Min (torr·sec/min)	4452	360
Corrected Ejection Time (sec)	0.314	0.020
Systolic Pressure x Heart Rate x 10^2	238	13
Minute Ventilation BTPS (liters/min)	5.7	0.4
Respiratory Rate (breaths/min)	14	1.4
R (Respiratory Exchange Ratio)	0.89	0.02
Oxygen Uptake (ml/kg)	5.79	0.27
Rectal Temperature (°C)	38.1	0.1
Coronary Blood Flow (ml/min/100 g)	121	6.1

(CONTINUED ON NEXT PAGE)

TABLE 12 (Continued)

CONTROL VALUES FOR VARIOUS CARDIORESPIRATORY MEASUREMENTS
(DUPLICATE VALUES AT 15-MIN INTERVALS IN 16 ANIMALS
WITH A MEAN WEIGHT OF 23.0 KG)

	Mean	±SE
Coronary Sinus Pressure, Mean (torr)	2.9	0.7
Coronary Vascular Resistance (dynes·sec/cm^5)	785	47
Left Ventricular Oxygen Uptake (ml/100 g/min)	15.7	0.8
Total Left Ventricular O_2/Total Body O_2	13.1	0.4
Left Ventricular Respiratory Ratio	0.90	0.03
Total Left Ventricular Oxygen Uptake (ml/min)	18.9	1.3
Total CBF/CO	3.8	0.2
Left Ventricular Efficiency (%)	21.8	1.6
Arterial Blood Values:		
Hemoglobin (g/dl)	13.3	0.3
Hematocrit (%)	40.0	0.8
Lactate (mg/dl)	18.2	0.7
Bicarbonate (mM/liter)	44.0	1.0
Plasma Proteins (g/dl)	5.0	0.1
HbCO (g/dl)	0.53	0.03
Oxygen Content (ml/dl)	17.4	0.4
Carbon Dioxide Content (ml/dl)	44.0	1.0
pH	7.330	0.010
P_{O_2} (torr)	83	1.9
P_{CO_2} (torr)	33.0	2.0
Oxygen Saturation (%)	91	1.5
Mixed Venous O_2 Content (ml/dl)	13.3	0.3
Coronary Sinus Blood Values:		
Hematocrit (%)	41.0	0.8
Plasma Proteins (g/dl)	5.1	0.1
Lactate (mg/dl)	15.8	0.6
HbCO (g/dl)	0.52	0.03

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TABLE 12 (Continued)

CONTROL VALUES FOR VARIOUS CARDIORESPIRATORY MEASUREMENTS
(DUPLICATE VALUES AT 15-MIN INTERVALS IN 16 ANIMALS
WITH A MEAN WEIGHT OF 23.0 KG)

	Mean	±SE
Coronary Sinus Blood Values (continued):		
Oxygen Content (ml/dl)	4.4	0.33
Carbon Dioxide Content (ml/dl)	5.6	1.0
pH	7.275	0.008
P_{O_2} (torr)	24.0	0.7
P_{CO_2} (torr)	47.9	2.1
Oxygen Saturation (%)	22.0	2.5
Extraction Ratios:		
Oxygen	0.75	0.02
Lactate	0.14	0.06

although heart rate increased with a consequent decrease in stroke output. No other significant changes in cardiac dynamics were observed. Ventilation increased slightly with increased levels of HbCO, as did the respiratory rate. There was a slight concomitant increase in oxygen uptake but the change was statistically insignificant. There were major changes in coronary and systemic oxygen tensions and oxygen saturations (Table 11 and Figs. 11 to 15). Myocardial oxygen uptake increased at the lower levels of HbCO but decreased at the highest level (35.6%).

b. Discussion: Several options are available to the mammalian cardiopulmonary system on exposure to carboxyhemoglobin hypoxia. There could be an increase in regional blood flow, a decrease in oxygen consumption, or an increase in oxygen extraction by the tissue without an increase in flow. The first and third options appear to be the most acceptable of these adaptative mechanisms, although the latter would be the least desirable since it would subject the tissues to lowered oxygen tensions. The various tissues of the body must receive oxygen at a rate adequate to sustain normal function. Aerobic metabolic processes depend on the maintenance of tissue P_{O_2} above some critical level. Tissue P_{O_2} is difficult to measure directly but changes in capillary P_{O_2} may, other things being equal, reflect changes in tissue oxygen tension. If there are no vascular shunts, the P_{O_2} of the venous blood draining a tissue is equal to the P_{O_2} at the venous end of its capillaries. Consequently, the P_{O_2} of the venous blood is a rough indicator of the adequacy of tissue oxygenation. The linear decline in coronary sinus venous blood P_{O_2} with increasing levels of HbCO (Fig. 11) indicates that there is a significant degree of venous

hypoxemia. This effect of carbon monoxide was compensated at the lower levels of HbCO by increases in coronary blood flow. There was a suggestion that this increase in flow was insufficient at the highest levels of HbCO and consequently the myocardial P_{O_2} decreased even further and left ventricle oxygen consumption decreased to the greatest extent. Oxygen delivery was apparently reaching a critical level when HbCO levels were approximately 35%. Coronary blood flow was not being increased sufficiently to counteract the influence of carbon monoxide on shifting the oxygen dissociation curve to the left. This was further evidenced (Fig. 15) by the marked decrease in myocardial arteriovenous differences. There was also a significant decrease in arterial oxygen tension following carbon monoxide inhalation, related probably to the leftward shift of the oxyhemoglobin dissociation curve. The hyperventilation observed may have augmented the leftward shift. The presence of this arterial hypoxemia may have accentuated the tissue hypoxia.

The present data definitely indicated that the myocardial effects consequent to carbon monoxide inhalation were more profound than the systemic effects. The decreased coronary arteriovenous oxygen difference, the lowered coronary sinus P_{O_2}, and the increased coronary blood flow are suggestive of the potential difficulties that this contaminant may impose on hearts that are not normal.

(2) *Chronically Exposed Animals*

Animals were exposed chronically to carbon monoxide. Each animal was exposed to 100 ppm CO for four hours each day five days a week over a six week period. It was anticipated that after such exposures the animals would have developed some degree of acclimatization to CO or some deleterious changes would have occurred. Following their last exposure the dogs were anesthetized and underwent the same test procedures as described earlier (subsection (b) GENERAL METHODS) except that they were tested at only one level of HbCO similar to that to which they had been chronically exposed.

a. Results: Table 13 presents the mean HbCO levels in these animals during their chronic exposures. Carboxyhemoglobin levels at the end of four hours were 10.54%. Their HbCO levels had returned to their normal control levels, approximately 0.4%, before they were again exposed to the higher ambient CO environment. There was no carry over of the body burden of CO from one exposure to the succeeding one. There was a slight tendency for the pre-exposure HbCO levels to be lower with time but the differences were not statistically significant. There were small and significant increases in hemoglobin and hematocrit by the end of the six weeks. However neither total blood volume nor red cell mass were significantly changed by the repeat exposures (Table 14). The major results of the acute tests to a level of HbCO equivalent to the levels found during the repeat daily exposure are represented in Table 15. The responses were similar to those observed in control animals given the same amount of carbon monoxide (Table 13).

TABLE 13

CARBOXYHEMOGLOBIN LEVELS DURING SUCCESSIVE DAYS OF 4-HOUR EXPOSURES TO 100 ppm CARBON MONOXIDE

Day*	%HbCO	
	Before	After 4 Hours
0	0.58	0.50†
1	0.63	10.75
3	0.63	10.66
10	0.50	10.07
13	0.52	10.41
14	0.25	11.40
18	0.26	9.91
19	0.27	9.00
24	0.45	10.64
28	0.49	10.13
29	0.42	12.43
Mean	0.44	10.54
SE	±0.04	±0.27

* Exposed 5 days per week over 6 weeks.

† In chamber — no CO in chamber.

TABLE 14

BLOOD VOLUMES IN CONTROL AND CHRONICALLY EXPOSED ANIMALS
EXPOSED TO 100 ppm CO 4 HOURS PER DAY 5 DAYS EACH WEEK FOR 6 WEEKS

	Exposed to CO		Not Exposed to CO	
	Control	Change After 6 Weeks	Control	Change After 2-21 Days
Number	6	6	6	6
Weight (kg)	25.27	1.24	28.4	0.0
F_{cell} Ratio	1.022	-0.055	1.078	0.021
Ht_c, W.B. (%)	36.13	1.14	40.60	0.20
Ht_c, P.V. (%)	35.30	3.15*	37.60	0.60
Hb (g%)	11.75	1.62†	12.40	-0.30
V_{RBC} (ml)	798	20	981	-1
V_{plasma} (ml)	1355	-17	1424	41
V_{blood} (ml)	2153	-41	2405	43

* Significant at 0.05% level.

† Significant at 0.01% level.

b. Discussion: Chronic exposure to 100 ppm CO for 4 hours each day was apparently insufficient to induce cardiovascular responses different from those in control animals not exposed to ambient carbon monoxide. No electrocardiograph changes were noted and the heart on gross examination was normal. It is possible that the duration of chronic exposure to CO was insufficient to induce significant changes in the myocardium and so altering the response to this level (10%) of carboxyhemoglobin. Additional studies at higher levels of ambient carbon monoxide or more prolonged exposure to 100 ppm would be needed not only to determine if acclimation occurs but what cardiovascular responses consequent to acclimation would occur.

TABLE 15

CARDIOVASCULAR CHANGES TO ACUTE CO EXPOSURE*
IN ANIMALS PREVIOUSLY EXPOSED TO 100 ppm CO DAILY FOR 6 WEEKS

	Control	Post CO Inhalation	
		7.5 Minutes	22.5 Minutes
%HbCO	0.4	10.0†	9.0†
Cardiac Output (liters/min)	3.84	3.82	3.82
Heart Rate (beats/min)	140	149§	151§
CBF (ml/100 g/min)	145	179†	193§

* Techniques and procedures similar to those employed to secure data in Tables 10 and 11.

† Significant at 0.01% level.

§ Significant at 0.05% level.

(3) Acute and Maintenance Exposed Animals

A preliminary study* was conducted on six animals to determine the influence on the cardiovascular system of a sudden exposure to carbon monoxide (raising the level of HbCO to approximately 6% and then remaining in that contaminated environment for another hour with the carboxyhemoglobin level being maintained at this level). The general methods employed in this study were similar to those described for Section *(1)*. Carboxyhemoglobin levels were raised to 6.5% and were maintained at approximately 6% for the remainder of the exposure. The results are presented in Table 16. There are several interesting aspects in that the heart rate gradually increased with time while cardiac index remained relatively constant with a consequent decrease in stroke volume. Coronary blood flow increased 29% and was maintained at this level for the duration of the exposure. Coronary sinus and arterial P_{O_2} both decreased. The effects on the myocardium were similar to those observed in the acute exposure to equivalent levels of HbCO (Section *(1)*). Ventilation also increased progressively. No other parameters were significantly altered. This preliminary study suggests the need for additional investigation of these effects with both lower and higher levels of carboxyhemoglobin. No conclusion, due to the limited number of animals employed, can be drawn, even though some

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* This was performed with the intent that it would serve as a basis for further investigation. It was not supported completely by funds from the ARB. The data suggests that further investigation is warranted if we can obtain financial support for its completion.

TABLE 16

CARDIOVASCULAR RESPONSES TO SUDDEN ELEVATION OF HbCO AND MAINTENANCE AT THIS LEVEL FOR ANOTHER HOUR

Parameter	Control	Post CO Administration (min)			
		0-15	16-30	31-45	46-60
1. Cardiac Index (liters/m^2)	3.51	3.33	3.26	3.19	3.68
2. Heart Rate (beats/min)	95	114	129	175	174
3. Left Ventricular Pressures (torr)					
Systolic	139.5	154.5	149.0	142.0	137.0
End Diastolic	3.5	1.7	3.0	3.5	-1.0
Mean	50.8	63.0	59.8	61.5	61.3
4. Femoral Arterial Pressures (torr)					
Systolic	118.0	127.5	118.5	119.0	116.5
Diastolic	83.0	89.5	86.0	86.0	87.3
Mean	90.0	104.5	97.0	97.5	94.5
5. Right Ventricular Pressures (torr)					
Systolic	35.7	31.9	30.3	35.5	38.1
End Diastolic	-2.4	-4.0	-3.6	-6.1	-9.5
Mean	8.1	7.1	8.1	8.6	25.0
6. Total Peripheral Resistance (dynes·sec/cm^5)	33.8	41.3	39.2	40.2	26.6
7. Arterial Blood					
pH	7.31	7.32	7.31	7.32	7.34
O_2 Tension (P_{O_2}) (torr)	86	61	61	69	66
CO_2 Tension (P_{CO_2}) (torr)	39.4	39.2	37.9	39.1	35.0
Hemoglobin (g%)	12.2	12.5	12.6	12.9	13.2
O_2 Saturation (%)	91.2	82.0	82.1	83.4	83.1
%HbCO	0.55	6.47	6.15	5.88	5.76

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TABLE 16 (Continued)

CARDIOVASCULAR RESPONSES TO SUDDEN ELEVATION OF HbCO AND MAINTENANCE AT THIS LEVEL FOR ANOTHER HOUR

Parameter	Control	Post CO Administration (min)			
		0-15	16-30	31-45	46-60
8. Coronary Sinus Blood					
pH	7.27	7.29	7.29	7.29	7.31
O_2 Tension (P_{O_2}) (torr)	26	19	21	22	20
CO_2 Tension (P_{CO_2}) (torr)	52.4	49.2	49.0	46.7	42.7
9. Coronary Blood Flow (ml/100 g/min)	132.8	172.3	176.9	175.9	168.0
10. Left Ventricular O_2 Consumption (ml/100 g/min)	14.81	16.82	21.99	18.56	19.15
11. Left Ventricular RQ	0.93	0.84	0.83	0.73	0.49
12. Systolic Ejection Period (msec)	221	210	178	185	183
13. Left Ventricular Work ($kg \cdot m/min/m^2$)	4.52	4.82	4.52	4.44	6.32
14. Coronary Vascular Resistance ($dynes \cdot sec/cm^5$)	903	808	796	738	749
15. Ventilation (liters/min)	2.87	3.10	3.38	3.46	4.66
16. Respiratory Rate (breaths/min)	---	9	10	9	13
17. Oxygen Consumption (ml/min)	140	122	125	153	178
18. Respiratory Ratio	0.73	0.79	0.77	0.71	0.75

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TABLE 16 (Continued)

CARDIOVASCULAR RESPONSES TO SUDDEN ELEVATION OF HbCO AND MAINTENANCE AT THIS LEVEL FOR ANOTHER HOUR

Parameter	Control	Post CO Administration (min)			
		0-15	16-30	31-45	46-60
19. Arterial Lactate (mg%)	16.6	14.6	19.2	14.1	13.2
20. Coronary Sinus Lactate (mg%)	14.9	13.3	21.2	16.4	16.6

suggestive changes did occur. It was of some interest that the changes in myocardial oxygen delivery remained constant during the prolonged period of maintained HbCO, suggesting that carbon monoxide hypoxia produces a sustained response on the heart.

(4) Acute Exposure of Myocardially Damaged Animals

The surgical implantation of electronic pacemakers in patients with complete atrioventricular (A-V) block has prevented sudden deaths and the morbidity associated with Adams-Stokes attacks. This change in the natural history of a once fatal disease is attributed to an improvement in cardiac function. Patients with chronic acquired complete heart block have abnormally low cardiac outputs. During temporary pacing with an electrode catheter placed in the right ventricle, the cardiac output increases to near normal but with continued pacing this increase is not maintained. The response of these patients to carbon monoxide inhalation has not been determined. It would be of considerable value to determine if carbon monoxide intoxication would alter their functional state.

a. Methods: Steiner and Kovalik developed a simple method of producing total heart block (atrioventricular block) in dogs. Complete heart block was produced in six dogs (mean weight 33.7 kg and a mean left ventricle mass of 158 g). Figure 16 illustrates the electrocardiographic changes produced. A permanent rechargeable cardiac pacemaker* was then implanted. The response to this pacing is shown in Fig. 16. Cardiac pacers were in place for a mean of 116 days (44-151). Pacers were recharged weekly. The animals response to a fixed load of carboxyhemoglobin (7.4 to 6.6%) was evaluated. The methods utilized in this investigation were similar to those employed in our other studies. Cardiorespiratory studies were performed while animals breathing filtered air were paced by the pacer followed by a period when the pacer was disconnected and the animals were on their own intrinsic rhythm. The

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* Pacers kindly supplied by Dr. J. Schulman of Pacemaker Systems Inc. Sylmar, Calif.

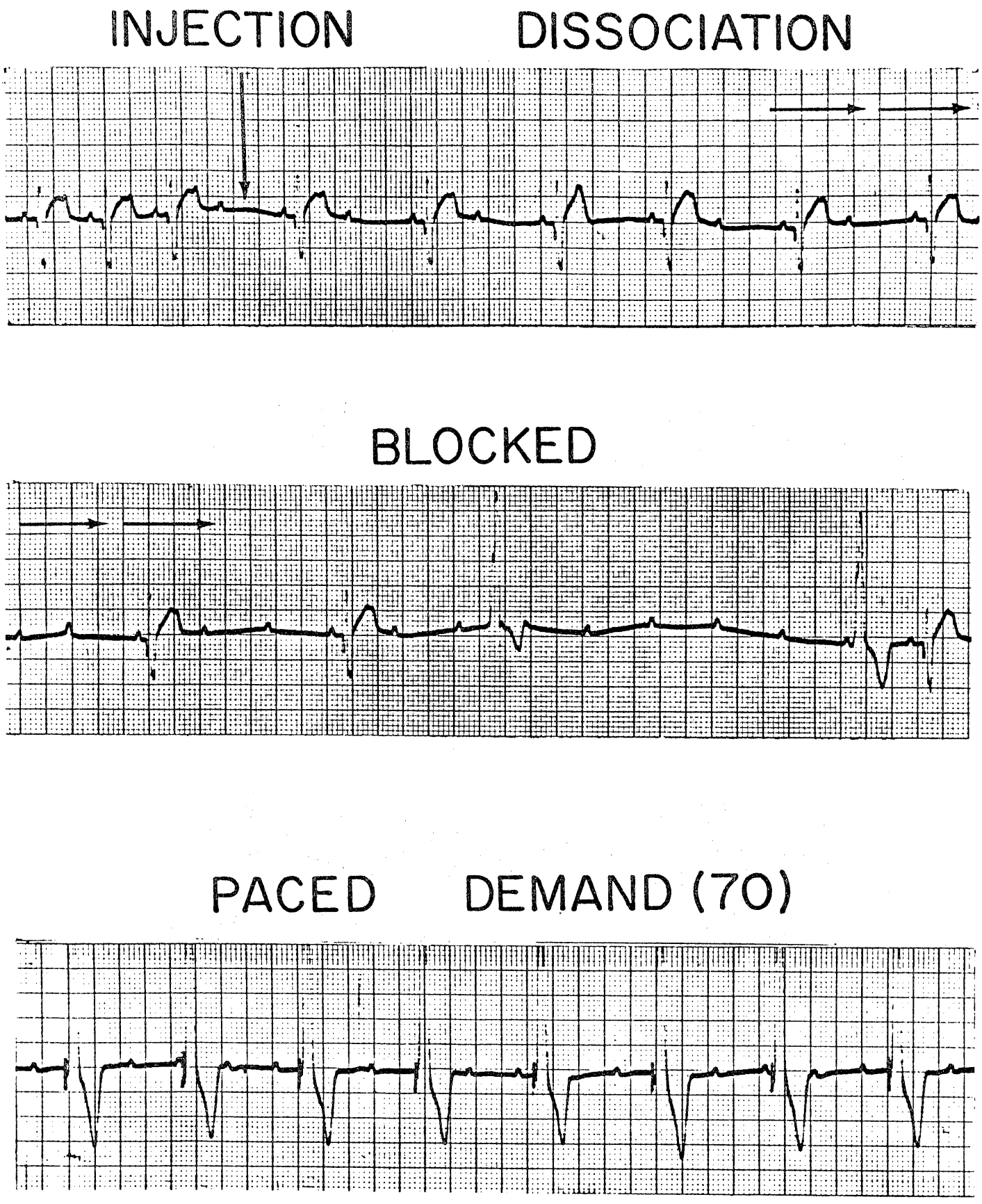

FIGURE 16

Production of Complete Heart Block and the Regulation of Ventricular Rate by a Demand Pacemaker. Note the Impulse Artifact in Lower Sector.

animals were then given CO and restudied while their hearts were again either paced or unpaced.

b. Results: Table 17 summarizes the results obtained. Cardiac output was low even when the hearts were paced (See Table 12 for normal dogs) and declined further when pacing was discontinued. Coronary blood flow was also much lower in these animals than in normal controls (Table 12) regardless of whether the heart was paced or not paced. Left ventricle mean pressure, left ventricle work, and the index of myocardial perfusion (heart rate × arterial systolic pressure) all decreased when animals' hearts responded to their own intrinsic rhythm. The slight decrease in coronary blood flow was not significant. In contrast to normal animals, coronary blood flow of the paced dogs to 7.4% HbCO remained constant. No other cardiac or respiratory changes were noted. When the pacemaker was disconnected coronary blood was again unaltered. However, cardiac output remained at the same level as during pacing in contrast to the fall observed while breathing filtered air. Arterial and coronary sinus P_{O_2} was unchanged. No respiratory or cardiac changes in response to increased HbCO were noted.

c. Discussion: The failure to increase coronary blood flow or to significantly lower blood gas tensions consequent to the presence of a modest level of carboxyhemoglobin was a surprising observation. Although it cannot be determined if secondary effects on the cardiovascular system resulting in increased strain on the myocardium occurred, the failure to increase coronary blood flow can be considered suggestive of producing a potential dangerous condition for this impaired heart. The inability to respond to hypoxia could result in further failure of the myocardium.

TABLE 17

CARDIORESPIRATORY RESPONSES OF ANIMALS WITH COMPLETE HEART BLOCK

	Filtered Air		CO Bolus	
	Paced	Unpaced	Paced	Unpaced
Arterial %HbCO	0.60	0.56	7.37✓	6.58✓
Cardiac Index (liters/$m^2 \cdot min^{-1}$)	2.26	1.80*	2.09	2.03
Heart Rate (beats/min)	74	52*	75	55*
Left Ventricular Systolic Pressure (torr)	154	149	154	146
Left Ventricular End Diastolic Pressure (torr)	6.0	6.5	5.0	5.2
Left Ventricular Mean Pressure (torr)	37.0	30.0†	34.0	29.0
Right Ventricular Systolic Pressure (torr)	55.8	52.5	56.0	53.8
Right Ventricular End Diastolic Pressure (torr)	1.7	2.7	1.2	1.5
Arterial Systolic Pressure (torr)	183	180	188	178
Arterial Diastolic Pressure (torr)	96	89	101	92
Left Ventricular Work ($kg \cdot m/min/m^2$)	4.56	3.54*	4.22	3.88
Heart Rate x Systolic Pressure x 10^2	135	94*	140	104*§
Left Ventricular Efficiency (%)	11.0	11.5	12.0	11.7
Coronary Blood Flow (ml/100 g/min)	97	82	80	80
Left Ventricular Oxygen Uptake (ml/kg)	12.2	15.0	11.9	11.9
Arterial O_2 Content (ml/dl)	18.9	19.8	19.5	20.4
Arterial P_{O_2} (torr)	73.9	74.6	76.9	79.7

(CONTINUED ON NEXT PAGE)

* $P < 0.05$.

† $P < 0.01$.

§ Diff. at 0.05 from non CO.

✓ Diff. at 0.01 from non CO.

TABLE 17 (Continued)

CARDIORESPIRATORY RESPONSES OF ANIMALS WITH COMPLETE HEART BLOCK

	Filtered Air		CO Bolus	
	Paced	Unpaced	Paced	Unpaced
Coronary Sinus O_2 Content (ml/dl)	4.2	3.8	4.3	5.0
Coronary Sinus P_{O_2} (torr)	22.3	18.4	17.1	20.0
Left Ventricular + dp/dt (torr/sec)	3467	3667	3637	4035
Left Ventricular - dp/dt (torr/sec)	3787	3310	4802	3820
Right Ventricular + dp/dt (torr/sec)	1181	1149	1100	1165
Right Ventricular - dp/dt (torr/sec)	998	1079	846	965
Oxygen Uptake (ml/kg·min)	4.52	4.70	5.62	5.20
Ventilation (liters/min)	5.66	5.52	6.59	7.00

(5) General Discussion

The potential deleterious influence of carbon monoxide inhalation on man's survival has been demonstrated by Heckter and Goldsmith (26) who performed a regression analysis of daily mortality in Los Angeles County and demonstrated a significant association between CO concentrations and mortality. The estimated contribution to mortality for an average ambient CO concentration of 20.2 ppm as compared to 7.3 ppm was 11 deaths for the days of the higher concentrations. Astrup et al. (27) have shown a pronounced effect of carbon monoxide inhalation on fetal development and neonatal death rate. Carbon monoxide is also suspected of having a role in artherogenesis (4). Studies on patients with angina after exposure to freeway driving where ambient CO levels averaged 53 ppm inducing arterial COHb levels of 5.08% showed that there was a significant decrease in exercise performance until angina, in systolic blood pressure times heart rate at angina and a decreased exercise heart rate at occurrence of angina (3, 4). Carbon monoxide exposure aggravates anginal pains. Approximately similar findings were reported by Anderson et al. (2). Previously, Ayres et al. (5-7) had demonstrated that carbon monoxide inhalation induced increases in cardiac output, and coronary blood flow with concomitant decreases in arterial and coronary sinus oxygen tensions. The increased coronary blood flow restores myocardial oxygen delivery toward normal. Adams et al. (1) also found that low (up to 20%) concentrations of HbCO increased coronary blood flow.

Although there is general agreement as to the increased coronary blood flow in normal animals in our studies and those of Ayres and Adams, there are differences in the magnitude of the response. These are

primarily related to the different procedures employed to elevate blood carboxyhemoglobin. Each of the three groups has given carbon monoxide to their animals by a different method. Other differences between the reported studies such as in cardiac output, ventilation and oxygen tension changes might also be attributed to the techniques employed. However, additional studies will be needed before these differences can be reconciled.

The most suggestive data from the present series of experiments developed from the studies on the heart block animals. The inability of these animals to respond to carboxyhemoglobin induced hypoxia by increasing their coronary blood flow raises important questions as to the hazards of ambient carbon monoxide on individuals with cardiovascular abnormalities. It was the first direct demonstration that cardiac diseased animals could not increase their blood flow and offered primary evidence supporting the observations made on CHD patients which had suggested that coronary blood flow or increased oxygen extraction failed to adequately respond to an increased level of blood carboxyhemoglobin.

The effect of carbon monoxide is through interference with transport and delivery of oxygen to the tissues, vital organs having high oxygen demand being especially vunerable. The most vunerable organs are the heart muscle (myocardium) and the brain. The hazard from carbon monoxide may be increased by any condition in which oxygen supply to tissues is already compromised. Adjustment of normal animals to this stress involves an increase in blood flow to provide more arterial blood per unit of time. If there is a reduction in this compensatory adjustment because of vascular disease, then such

animals will be at special risk from small concentrations of carbon monoxide. The data presented in this report support these basic concepts for both normal and cardiac diseased animals.

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INDEX OF TERMS

CARDIOVASCULAR MEASUREMENTS

Parameter and Formula	Abbreviation	Units
1. Cardiac Output	CO	ml/min
2. Heart Rate	HR	beats/min
3. Left Ventricular Pressures		
Systolic	LVSP	torr*
End Diastolic	LVEDP	torr
Mean	LV$\bar{X}$P	torr
Peak + dp/dt	LV+D	torr/sec
Peak - dp/dt	LV-D	torr/sec
Pulse	LVPP	torr
4. Right Ventricular Pressures		
Systolic	RVSP	torr
End Diastolic	RVEDP	torr
Mean	RV$\bar{X}$P	torr
Peak + dp/dt	RV+D	torr/sec
Peak - dp/dt	RV-D	torr/sec
Pulse	RVPP	torr
5. Arterial Pressures		
Systolic	ASP	torr
Diastolic	ADP	torr

*Equivalent at sea level to mm Hg.

Parameter and Formula	Abbreviation	Units
5. Arterial Pressures (continued)		
Mean	$A\bar{X}P$	torr
Peak + dp/dt	A+D	torr/sec
Peak - dp/dt	A-D	torr/sec
Pulse	APP	torr
6. Pulmonary Artery Pressures		
Systolic	PASP	torr
Diastolic	PADP	torr
Mean	$PA\bar{X}P$	torr
Peak + dp/dt	PA+D	torr/sec
Peak - dp/dt	PA-D	torr/sec
Pulse	PAPP	torr
Wedge	PAWP	torr
7. Cardiac Index $\frac{\text{Cardiac Output}}{1000 \times \text{Body Surface Area}}$	CI	liters/min/m^2
8. Stroke Volume $\frac{\text{Cardiac Output}}{\text{Heart Rate}}$ or $\frac{CO}{HR}$	SV	ml/beat
9. Stroke Index $\frac{\text{Stroke Volume}}{\text{Body Surface Area}}$ or $\frac{SV}{BSA}$	SI	ml/beat/m^2

Parameter and Formula	Abbreviation	Units
10. Total Peripheral Resistance $\frac{A\bar{X}P - RVEDP \cdot 1332}{CO/60}$	TPR	dynes-sec-cm^5
11. Total Pulmonary Resistance $\frac{PA\bar{X}P - LVEDP \cdot 1332}{CO/60}$	TPLR	dynes-sec-cm^5
12. Mean Systolic Ejection Rate SI/SEP	$\bar{X}$SER	ml/m^2/sec
13. Tension Time Index/B LVSP x SEP	TTIB	torr-sec/beat or pressure time/beat
14. Tension Time Index/Min LVSP x SEP x HR	TTIM	torr-sec/min or pressure time/min
15. Left Ventricular Work $CI \times \frac{1.36}{100} \times LVSP - LVEDP$	LVW	kg·m/min/m^2
16. Left Ventricular Stroke Work $\frac{LVW}{HR} \times 1000$	LVSW	g·m/beat/m^2

Parameter and Formula	Abbreviation	Units
17. Left Ventricular Stroke Power $\frac{LVSW}{SEP}$	LVSPW	$g \cdot m/beat/m^2/sys\ sec$ or $g \cdot m^2/sys\ sec$
18. Corrected Ejection Time $\frac{SEP}{\sqrt{60/HR}}$	CET	sec
19. First Differential Index A $\frac{LV + dp/dt}{LVW}$	Diff A	$torr/sec/kg \cdot m/min/m^2$
20. First Differential Index B $\frac{LV + dp/dt}{LVSP}$	Diff B	torr/sec/torr
21. Coronary Blood Flow	CBF	ml/100 g/min
22. Mean Coronary Sinus Pressure	$CS\bar{X}P$	torr
23. "Left" Coronary Resistance $\frac{A\bar{X}P - CS\bar{X}P \cdot 1332}{CBF \times \frac{LV\ Mass}{100}}{60}$	CVR	$dynes\text{-}sec\text{-}cm^5$

Parameter and Formula	Abbreviation	Units
24. Total Left Ventricular Mass	LV Mass	g

$$\frac{4.70}{\text{Wt (kg)}} \times 1000$$

25. Total Left Ventricular Coronary Blood Flow	LVCBF	ml/min

$$\text{CBF} \times \left(\frac{\text{LV Mass}}{100} \right)$$

26. Total Coronary Blood Flow	TCBF	ml/min

$$\text{CBF} \times \left(\frac{\text{LV Mass}}{100} \right) \times 1.5$$

27. CBF Percent of CO	CBF%	%

$$\frac{\text{TCBF}}{\text{CO}} \times 100$$

28. Rate x Pressure	RxP	torr/min

$$\frac{\text{HR}}{100} \times \text{ASP}$$

Parameter and Formula	Abbreviation	Units
29. Diastolic Pressure Tension Index	DPTI	torr·sec/beat

$$\int_{t_1}^{t_2} (\text{Aortic Press} - \text{LV Press})$$

Instantaneous from begin diastole t_1 to end t_2

or

Diastolic Interval x ($\overline{AXP}$ - $\overline{LVXP}$)

30.	Arterial Chemistry		
	A. Lactate	ALAC	mg/dl
	B. Free Fatty Acids	AFFA	mg/dl
	C. Glucose	ACHO	mg/dl
	D. Hemoglobin	AHb	g/dl
	E. Hematocrit	AHMCT	%
	F. Plasma Proteins	APP	g/dl
31.	Coronary Sinus Chemistry		
	A. Lactate	CSLAC	mg/dl
	B. Free Fatty Acids	CSFFA	mg/dl
	C. Glucose	CSCHO	mg/dl
	D. Hemoglobin	CSHb	g/dl
	E. Hematocrit	CSHMCT	%
	F. Plasma Proteins	CSPP	gm/dl

Parameter and Formula	Abbreviation	Units
32. Arterial Blood Gases		
A. Oxygen Content	AO_2	ml/dl
B. Carbon Dioxide Content	ACO_2	ml/dl
C. pH	ApH	units
D. Oxygen Tension	APO_2	torr
E. Carbon Dioxide Tension	$APCO_2$	torr
F. Carbon Monoxide Content	ACO	ml/dl
G. Percent Saturation O_2	HbO_2	%
$\frac{AO_2 \text{ Content ml/dl}}{1.39 \times \text{AHb g/dl}} \times 100$		
H. Bicarbonate (Total)	$AHCO_3$	mM/liter
ACO_2 mM/liter - CO_2 DISS mM/liter		
33. Coronary Sinus Gases		
A. Oxygen Content	CSO_2	ml/dl
B. Carbon Dioxide Content	$CSCO_2$	ml/dl
C. pH	CSpH	units
D. Oxygen Tension	$CSPO_2$	torr
E. Carbon Dioxide Tension	$CSPCO_2$	torr
F. Carbon Monoxide Content	CSCO	ml/dl
G. Percent Saturation O_2	HbO_2	%
$\frac{CSO_2 \text{ Content ml/dl}}{1.39 \times \text{CSHb g/dl}} \times 100$		
H. Bicarbonate (Total)	$CSHCO_3$	mM/liter
$CSCO_2$ mM/liter - $CSCO_2$ DISS mM/liter		

Parameter and Formula	Abbreviation	Units
34. Whole Body $\dot{V}_{O_2}$	$WB\dot{V}_{O_2}$	ml/min
35. Left Ventricular $\dot{V}_{O_2}$ (Total) $\left[AO_2 - CSO_2 \right] \left[\frac{LVCBF \times \frac{LV\ Mass}{100}}{100} \right]$	$TLV\dot{V}_{O_2}$	ml/min
36. Left Ventricular $\dot{V}_{O_2}$ Per 100 g $\left[AO_2 - CSO_2 \right] \left[\frac{LVCBF}{100} \right]$	$LV\dot{V}_{O_2}$	ml/100 g/min
37. Total Left Ventricular $\dot{V}_{O_2}$ As Percent $WB\dot{V}_{O_2}$ $\left[\frac{TLV\dot{V}_{O_2}}{WB\dot{V}_{O_2}} \times 100 \right]$	$TLV\dot{V}_{O_2}\%$	%
38. Total Myocardial $\dot{V}_{O_2}$ $\left[AO_2 - CSO_2 \right] \left[\frac{LVCBF \times \frac{LV\ Mass}{100}}{100} \right] \left[1.5 \right]$	$M\dot{V}_{O_2}$	ml/min
39. $M\dot{V}_{O_2}$ as Percent of $WB\dot{V}_{O_2}$ $\frac{M\dot{V}_{O_2}}{WB\dot{V}_{O_2}} \times 100$	$M\dot{V}_{O_2}\%$	%

Parameter and Formula	Abbreviation	Units
40. Left Ventricular Respiratory Quotient	LVRD	ratio

$$\frac{\left(CSCO_2 - ACO_2 \right) \left(\frac{CBF}{100} \right)}{LV\dot{V}O_2}$$

41. Total Left Ventricular Lactate Utilization	TLAC	mg/min

$$\left(ALAC - CSLAC \right) \left(\frac{CBF \times \frac{LV\ Mass}{100}}{100} \right)$$

42. Total Left Ventricular Glucose Utilization	TCHO	mg/min

$$\left(ACHO - CSCHO \right) \left(\frac{CBF \times \frac{LV\ Mass}{100}}{100} \right)$$

43. Total Left Ventricular FFA Utilization	TFFA	mg/min

$$\left(AFFA - CSFFA \right) \left(\frac{CBF \times \frac{LV\ Mass}{100}}{100} \right)$$

44. Left Ventricular Efficiency	LVEF	%

$$\frac{LVW}{TLV\dot{V}O_2 \times 2} \times 100$$

Parameter and Formula	Abbreviation	Units
45. Central Blood Volume	CBV	ml

$$\left[\left[\overline{X}tt - \left\{ \frac{60}{WDR} \times DS \right\} \right] \left[60 \right] \right]$$

$\overline{X}tt$ = $\overline{X}$ transit time (sec)

WDR = withdrawal rate (cc/min)

DS = sampling dead space (cc)

46. Myocardial Coefficient of Oxygen Extraction	MCO	ratio

$$\frac{AO_2 - CSO_2}{AO_2}$$

APPENDIX

EFFECTS OF CARBON MONOXIDE ON HUMAN BEHAVIOR

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A brief summary of the physiological and psychological effects of carbon monoxide on man and animals was given at a meeting called by the National Academy of Science in Washington D.C. It is presented here as an appendix to indicate the status of our knowledge on this pollutant as of October 1973.

* * *

Studies on behavioral effects of carbon monoxide poisoning have been conducted over approximately the same period of time as were physiological and pathological effects. Unfortunately, the preciseness and appropriateness of experimental procedures and the consequent results from the early behavioral studies were not of the same quality as those from the physiological field. These differences were, in part, related to inadequate understanding of the significance of behavioral changes, and the inability to distinguish between simple perceptual motor performance and the more complex performance involving sustained and/or selective attention, short-term memory and decision making among the possible alternatives, and finally the rather loose use and appreciation of the physiological mechanisms involved in carbon monoxide intoxication, and the failure to adequately exploit the physiological and psychological tools available. Even today some physiological and behavioral studies suffer from these

same inadequacies, i.e., the failure to precisely measure HbCO levels at various levels of exposure, the inability to distinguish between the physiological effects of CO bolus of high concentration or the slow insidious increment in HbCO over time with lower inhaled concentrations, the amount of CO brought to or removed from the blood by changes in alveolar ventilatory volumes, the influence of competing factors such as drugs, alcohol or prior exposure to CO, the small number of subjects, and most importantly the failure to adopt a proper experimental design which would produce statistically significant information. With all of these qualifications there still remain questions regarding behavioral testing itself. Factors such as the following partial listing must be considered in evaluating results from behavioral experiments - arousal state of subject during testing, subject-experimenter interreaction, subject-subject interreaction, task difficulty (complexity), task interest, task duration, single vs. multiple tests during exposure, motivation of subject, and influence of competing agents such as other drugs and chemicals with the agent being evaluated.

Sayers et al. (35) were among the first (1929) to make observations on the effects of automobile exhaust upon some psychomotor and psychological tasks. Hand-eye coordination and steadiness, tapping speed, arithmetic (continuous addition), location memory and simple reaction time showed no significant changes despite the presence of HbCO levels of approximately 20 to 30%. Similarly Forbes et al. (18) were unable to demonstrate in simulated driving tasks any deterioration of performance when HbCO levels were up to 25% and a small decrement

when HbCO levels were above 35%. The simplicity of the tests and the functional tests themselves probably precluded the possibility of demonstrating poorer performance.

Performance testing in automobiles driven on either public highways or enclosed tracks (34) demonstrated on a small number of subjects some decrement in performance parameters. The use of "bolus" injections of CO into the breathing system at intervals to maintain required HbCO levels may have induced some uncontrolled variables. Ramsey (32) also reported an increase in multiple-choice reaction times while driving in traffic where ambient CO levels ranged from 16 to 62 ppm. HbCO was not measured. It is doubtful that information of much value was secured from these practical situation studies.

McFarland et al. (27) in conjunction with their studies on altitude exposure were able to show that changes in visual threshold occurred at HbCO levels as low as 5%. These findings were confirmed by Halperin et al. (21) indicating that a measurable impairment in visual function was detectable when HbCO concentrations were 4 to 5%; greater impairment was noted at higher HbCO levels. A preliminary report by McFarland's group (28) on further studies of CO inhalation on the visual apparatus indicate that for glare recovery the dark adaptation final threshold values increase as HbCO levels increase from control to 6 to 17% HbCO. Peripheral recognition tasks are not affected until HbCO reaches 17%. Central and peripheral complex tasks are also not influenced by low levels of HbCO.

Similar levels of HbCO (5%) were found by Schulte (36) to induce significant decrements in ability to perform arithmetic problems, t-crossings, and discrimination of forms and color. He showed positive correlations between HbCO level (up to 20%) and performance decrement. It should be noted that these results were obtained during longer testing sessions than those employed in the studies by Dorcus and Weingand (36). The ability to judge slight differences in successive short time intervals correctly showed significant impairment when COHb levels were raised approximately 2 to 3% above background. These findings by Beard and Wertheim (7) suggesting an altered mental function represent the lowest levels of HbCO to produce a significant alteration in behavioral performance. During the past years they (8) have reported in preliminary form additional experiments related to the influence of small doses of CO upon cerebral functions. Their studies have shown significant reductions in vigilance and in performance on a task incorporating time estimation and motion, while arithmetic performance and a few others remained unaltered. These reduced performances were noted at HbCO levels of approximately 2%. However, when HbCO was at 7% the changes observed were not as marked. In our laboratory we have seen a similar response. The implications of these discrepancies at the higher HbCO levels remains unexplained.

Trouton and Eysenck (40) reported impairment in control precision and multiple limb coordination at HbCO levels of approximately 5%. O'Donnell et al. (29) were unable to confirm the above even though HbCO was as high as 12.7%. Grudzinska (20) evaluated the electroencephalograms (EEG) in subjects exposed to CO (the large variation in HbCO

levels (mean 7%) of these subjects exposed to 100 ppm should be noted). A significantly higher proportion of flat low voltage tracings were noted. Dinman (15) has reviewed the EEG data and also reported on his own findings. He failed to detect changes even though HbCO levels were approximately 27%. Improved methodological procedures for analyzing EEG data would be valuable in clarifying this issue.

It is quite likely that some of the performance decrement associated with CO exposure could be masked by the subject's attention to the given task. We (23) sought to determine if CO exposures which simulated those experienced by urban motorists in "normal" and polluted air (Los Angeles) affect the human ability for maintenance of a high level of vigilance in a monotonous environment. We studied 15 subjects trained to discriminate 1-second duration light pulses on the basis of stimulus brightness. The subjects performed the monitoring task for one hour. Blood samples for HbCO determinations were obtained at fixed intervals during the total two-hour exposure while breathing air containing 0, 26, or 111 ppm CO. The results are shown in Fig. A1. As anticipated, the subjects were unable to maintain their vigilance at the alerted level during the monitoring task. Their condition deteriorated during the hour-long vigil. The 0 and 26 ppm CO curves have similar patterns. However, subjects breathing 111 ppm had a significant deterioration when HbCO was around 5% and a further decline in signal detection at 6% HbCO. These findings have been confirmed by Beard and Wertheim (8) recently.

Other investigators have been unable to demonstrate comparable behavioral effects even though they have had subjects breathing higher

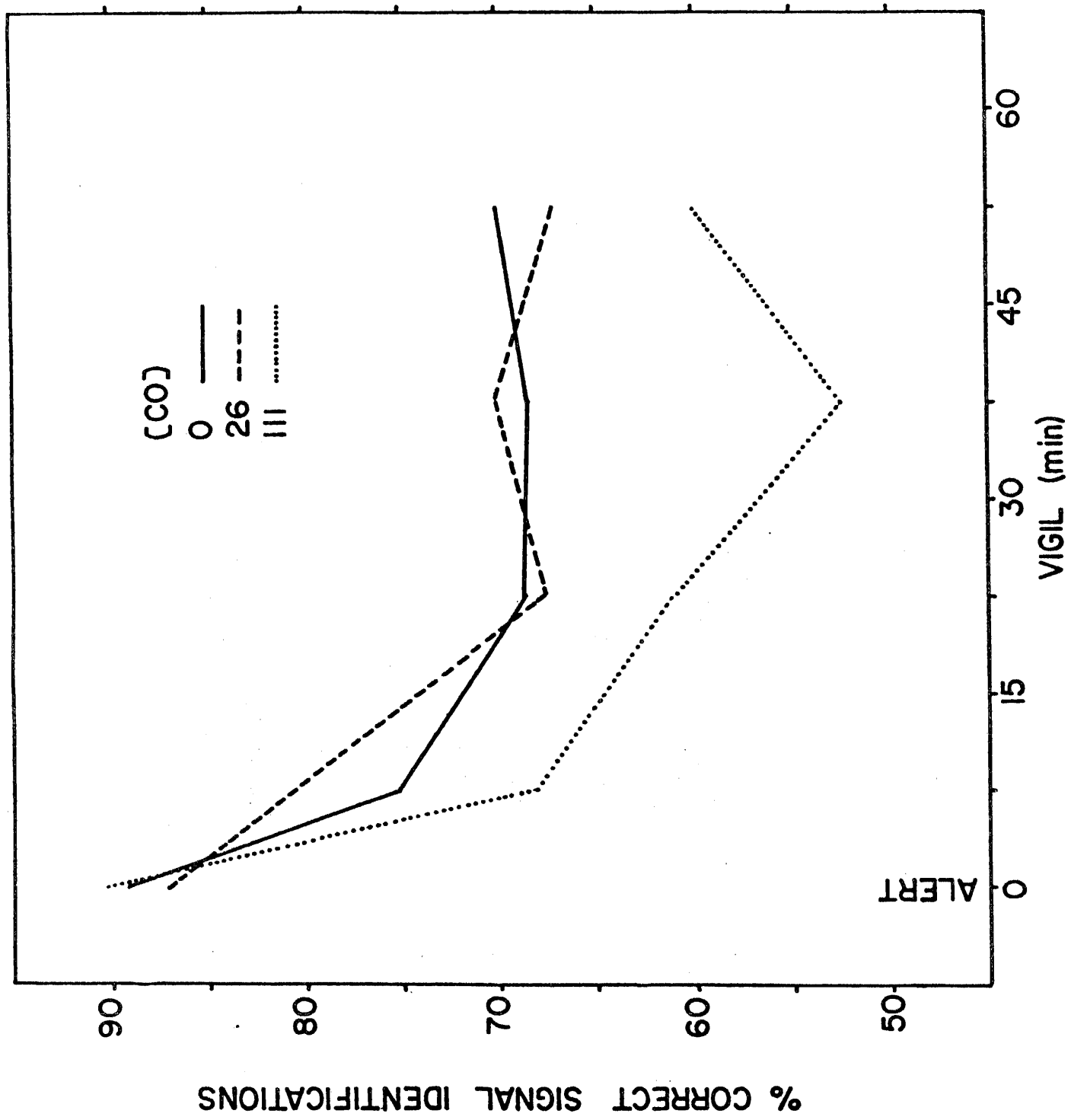

FIGURE A1

The Effects of Carbon Monoxide on Nonsmokers in the Alert Test.

concentrations of carbon monoxide. Stewart et al. (38), O'Donnell et al. (30, 39) and Mikulka et al. (26) have reported no behavioral impairment even, in some instances, when HbCO levels were 11 to 13%. My attempt to rationalize this discrepancy as a result of methodological differences has not been satisfactory. Nonetheless, both in our studies and those of Beard and Wertheim subjects were isolated in a small chamber and required to perform an extremely tedious task in a continuous or repetitious manner over a relatively long period. In the studies producing negative results, the subjects' tasks have been many and varied and they have been allowed ample free time for rest and recreation during the exposure period. CO exposures were also administered in a more commodious and, presumably, more interesting environment. Moreover, in some of these studies subjects were apparently tested in groups. If so, social interaction and, perhaps, a feeling of competition among the subjects may have sustained higher performance levels than would have been seen had the subjects been tested individually.

Although the available information appears to have some marked conflicts, there is a strong suggestion that the effects of CO on performance might be most severe when individuals are already required to resist monotony's stressful effects. In other words, the effects of CO and monotony may combine to produce greater impairment than that which follows exposure to either stressor alone.

Physical Work

It has become common in some areas to recommend that under certain smog conditions the physical activity of children and young adults be

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It has become common in some areas to recommend that under certain smog conditions the physical activity of children and young adults be

reduced or completely abolished. This rather stringent behavioral modification in response to an assumed health risk at urban levels of ambient CO may or may not be correct. Nonetheless, it has been appreciated for some time that individuals having a large burden of carbon monoxide experience difficulty in performing work. The subjects studied by Chiodi et al. (12) were unable to carry on tasks requiring low levels of physical exertion when their blood carboxyhemoglobin levels had reached 40 to 45%. In fact, several collapsed while attempting to conduct routine laboratory tasks. Wayne et al. (41) reported that Los Angeles runners performed at lower levels during races when photochemical smog was present. MacMillian (17) reported data suggesting that impaired swimming performance was associated with exposure to CO (30 ppm) originating from traffic. On the other hand, Holland et al. (22) were unable to find any change in energy requirements for light levels of work performed in a smog chamber for a short time period. Chevalier and co-workers (10, 11, 24) also utilizing a light work load of 5 minutes duration reported that while the oxygen uptake of work was not affected when HbCO levels were approximately 4%, there was a significant increase in oxygen debt when it was related to the total increased oxygen uptake. Five subjects studied by Pirnay et al. (31) performed work at an oxygen expenditure of 1.5 L/min for 15 minutes. No differences in oxygen uptake were found even though HbCO reached 15%. In a rather complex study where HbCO fluctuated between 5 to 27%, Klausen et al. (24) found no differences related to CO in energy expenditures when subjects worked for 15 minutes at 50% of their $\dot{V}_{O_2\ max}$. The wide variability in

experimental conditions, i.e., duration and magnitude of the exercise, the level of HbCO, the method of giving CO, the small number of subjects and their limited age range, make it difficult to precisely analyze the results. Work in progress at the Institute where subjects work for 4 hours at 35% of their maximal aerobic power while exposed to 50 ppm of CO will be discussed in a preliminary manner. Two groups of men, ages 18 to 30 and 40 to 55 years, comprised of both smokers and non-smokers, served as subjects for both the aerobic power and the sustained 4-hour work tests.

However, there appears to be little doubt that certain levels of HbCO markedly influence the aerobic power capacity (maximum oxygen uptake) (33). Most attention has been directed to the study of intermediate levels of HbCO (10 to 35%). It should be noted that these levels of were higher than those found in urban areas. In general, subjects were given CO to breathe for a period of time so as to attain the requisite blood levels prior to the test itself and the tests were of 2 to 6 minutes duration. The use of the "bolus" plus maintenance technique may have induced other changes which could have influenced the results. Fig. A2 presents a summary of the available information on the influence of different levels of HbCO on the maximum oxygen uptake. Although there are some deviations, there was, in general, a linear decline in $\dot{V}_{O_2\ max}$ with the progressive increase in HbCO levels. Data from the Institute on 20 men, half smokers and half non-smokers, are also shown. These men were exposed to 50 ppm CO during the test (total exposure time of 27 minutes) and the post-exercise HbCO's were 2.7 and 4.5% for non-smokers and smokers respectively. The mean decrease in $\dot{V}_{O_2\ max}$ of 3.3% was not significant. We have just completed a series of studies with young

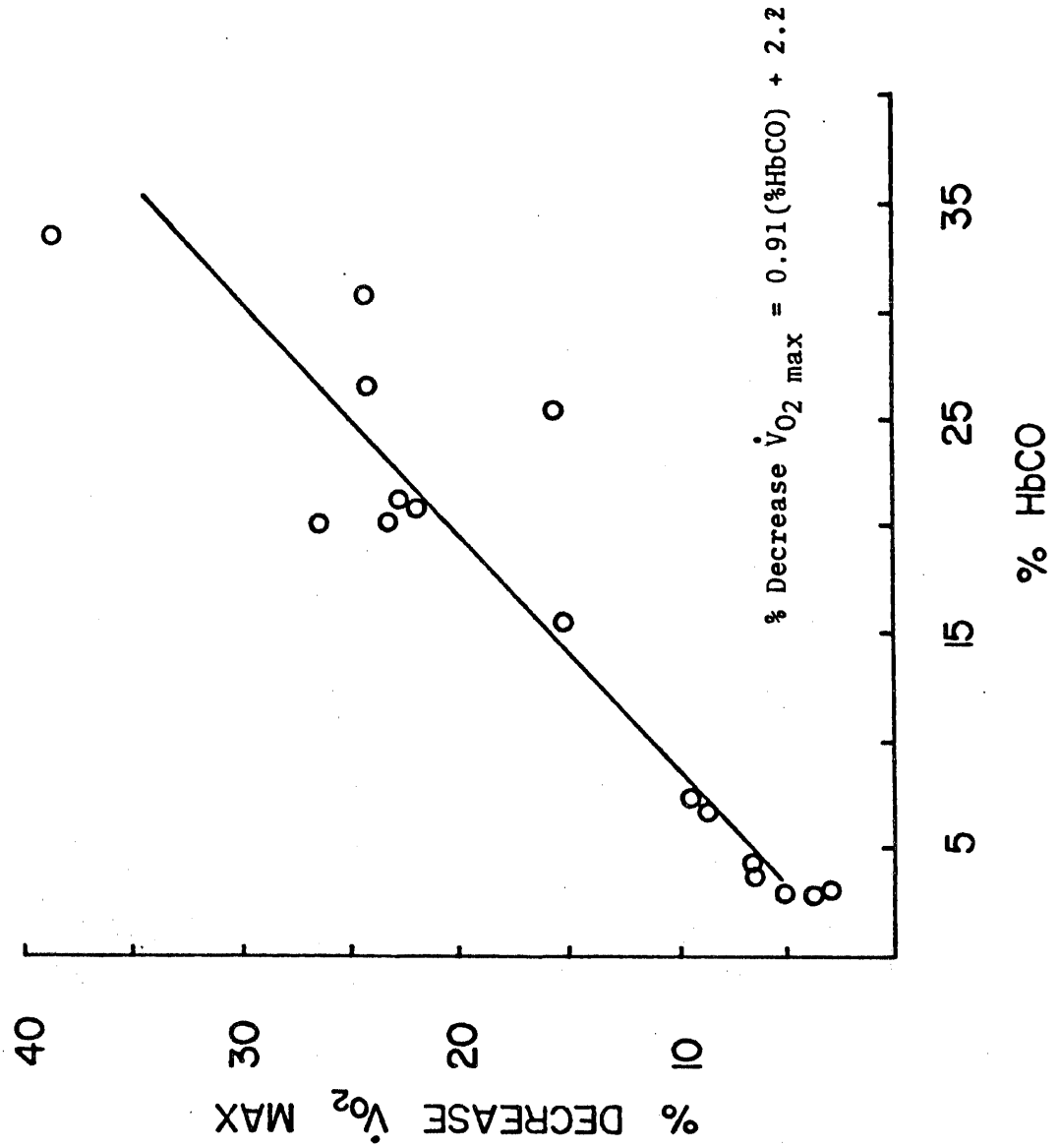

FIGURE A2

Relationship Between %HbCO and Decrement in Maximum Aerobic Power, the Linear Regression (% Decrease $\dot{V}_{O2\ max}$ = 0.91(%HbCO) + 2.2) Obtained Only From 5 to 36% HbCO.

non-smokers breathing 75 and 100 ppm CO and the decrement in $\dot{V}_{O_2\ max}$ was 4.4 and 7.0% respectively. (Data on older subjects has been collected and is in the process of being analyzed.) Their HbCO levels were in filtered air 0.26 and 3.40 and 4.37 respectively in the two levels of ambient carbon monoxide. Recalculation of data extracted from Chevalier's (10) studies indicated no change in $\dot{V}_{O_2\ max}$ between his smoking or non-smoking subjects. Unfortunately HbCO levels were not measured in these subjects, but in all probability the smokers had levels of between 2 and 4%. Therefore it would appear that the maxiumum aerobic power ($\dot{V}_{O_2\ max}$) of young subjects whether smokers or non-smokers was not impaired when breathing ambient air containing 50 to 75 ppm but that significant reductions can occur if higher levels are present.

Addendum

We have completed our studies on young men performing max tests in a 35°C environment. Although under these high ambient conditions the $\dot{V}_{O_2\ max}$ was decreased 4.3% from 25°C tests, CO inhalation did not induce any further decrease. HbCO levels were pre 0.9 and 2.6 and post 2.5 and 4.1% for non-smokers and smokers respectively.

Preliminary analyses of the $\dot{V}_{O_2\ max}$ data obtained on older subjects in our study have just been completed. These subjects had a decrease of 2.6% in their $\dot{V}_{O_2\ max}$ compared to the younger men when breathing 50 ppm CO. Probably the most interesting observation was the marked difference in $\dot{V}O2\ max$ between smokers and non-smokers (no such differences had been found between these groups in the younger subjects). Older smokers had $\dot{V}_{O_2\ max}$ values of 30.7 in contrast to the 38 ml/kg/min in the non-smoking group.

These differences are even more striking when one considers that these older smokers were the "cream of the crop." Only one of every two candidates in this group had successfully passed our screening examinations. Our older smokers also arrived at the laboratory with higher initial HbCO values - 4.54 against 3.17 of the younger group. Following their maximum aerobic capacity test in 50 ppm CO smokers had only a minimal increase in (4.6%) compared to an increase from 0.64 to 2.4% in the older non-smokers.

We have also incomplete data on the young subjects who were working for 4 hours at either 25 or 35°C breathing either filtered air or air containing 50 ppm CO. Oxygen uptake was similar under all four conditions (1.45 L/min). Cardiac output was not different during the CO exposures (12.0 L/min at 25°C and 14.0 L/min at 35°C). Heart rates during the walks at 25°C were constant up to the third hour (103) but increased in the fourth to 116. During the CO walks the heart rates for the first 3 hours were 108 rising to 128 in the fourth hour. The changes in HbCO during this work period are interesting. Non-smokers have initial levels of 0.55 falling to 0.31 when breathing filtered air and rising to 5.24% during the CO exposure. On the other hand, smokers had initial levels of 5.50 falling to 1.80 in filtered air and rising to 6.56 when breathing in an atmosphere containing 50 ppm CO. Similar studies on the older age group (40 to 55 years) are in progress and the data collection is too fragmentary for presentation.

Cardiovascular System

Statistical evidence that CO concentrations present in urban atmospheres can be responsible for aggravated heart disease problems has been available since 1938 (9). Goldsmith and his co-workers (13, 19)

presented statistical evidence that individuals hospitalized for heart attacks had a less favorable survival experience if they were from areas with relatively higher ambient CO concentrations. These studies suffer from some deficiencies in providing full and accurate presentation of other factors such as absolute levels of CO, duration of exposure, prior socioeconomic status, etc., which may well have influenced the statistical interpretations. However, several more recent studies lend some credence to the basic premise that the additional load of a decreased myocardial oxygen supply resulting from the presence of HbCO to an already compromised myocardium may indeed provide the impetus for a fatal consequence or at the least an intensification of symptoms. Aronow et al. (3) demonstrated in 10 patients with angina who had been subjected as passengers to a 90-minute trip on the freeway, that there occurred subsequently a significant decrease in exercise performance time until angina, and in SR index (systolic pressure x heart rate). Three of the 10 patients developed ischemic ST-segment depression while breathing freeway air. When these patients had been breathing compressed air on a similar excursion, no significant changes from control occurred. COHb levels averaged some 5% after the drive. However, there was wide variation in the individual values. Ambient CO in the moving car averaged 47 (range 37 to 61) ppm. Anderson et al.(2) conducted a similar study under rigorous laboratory conditions with two levels of ambient CO, 50 and 100 ppm, and with a 4-hour exposure. It was clearly demonstrated that small increases in HbCO, to 2.9 and 4.5%, (the control levels were slightly higher than anticipated) resulted in a more rapid onset of anginal pain during exercise as well as increasing the duration of the

pain after cessation of exercise. The contaminant conditions of Anderson's study were quite in line with the situation occurring in urban areas.

Permutt and Fahri (17) have calculated that, when HbCO levels were approximately 5%, resting coronary blood flow must increase some 20% in order to prevent myocardial ischemia. Klausen et al. (24) suggested on the basis of their investigations that tissue P_{O_2} may be reduced 18% in the presence of 15% $_{HbCO}$. The patients without coronary heart disease studied by Ayres et al. (4-6) were given a bolus of CO raising HbCO levels to 8.9%, and they showed an increased coronary blood flow (44%), decreased myocardial lactate extraction, a decreased central venous P_{O_2} (20%) and an increased cardiac output. However, patients with CHD under the same CO stress did not increase their coronary blood flow while still showing a decrease in the $P_{CS_{O_2}}$.

Studies conducted on animals (dogs) have been reported. As had been the case with the human studies, considerable variation in both the mode of administration and the quantities of CO given have precluded the development of a clear concept of the effects of CO on the cardiovascular system. Actually these studies represent the activity of three groups, Ayers et al. (4-6), Erickson et al. (1, 14) and ourselves. Several investigators have reported on the influence of cigarette smoking on coronary blood flow but they generally have not reported their HbCO levels.

The massive bolus technique has been employed by Ayers et al. whose animal and human subjects breathed over a period of 0.5 to 2.0 minutes a gas mixture containing 50,000 ppm CO or on a few occasions 1,000 ppm (peak? $_{HbCO}$ 7 to 34%). Erickson et al. provided their dogs with a gas mixture having 1,500 ppm CO for a period of 30 minutes (final HbCO 23.1%).

In our studies several different approaches to inducing CO poisoning were utilized - bolus, i.e., sufficient CO in 3 minutes to produce HbCO levels from 6.2 to 35.6% - continuous inhalation over 2 to 4 hours of CO either 50 or 100 ppm - bolus plus maintenance of 50 or 100 ppm CO - exposure to 50 or 100 ppm for 4 hours/day 5 days/week (12). Some of these studies are completed but not all data have been analyzed. Preliminary findings on some facets of our current studies will be presented. Cardiovascular responses to bolus CO can be briefly summarized as follows: increase in coronary blood flow, increases in heart rate, decreased $P_{A_{O_2}}$, decreased $P_{CS_{O_2}}$, decreased arterial O_2 saturation, increased LV_{O_2} uptake, no change in cardiac output or in LV dP/dt.

Although it may be premature to draw conclusions from the present state of knowledge, it was quite clear that all groups studying CBF in the dog agree that CBF and $P_{CS_{O_2}}$ decrease under the conditions of inducing increased HbCO utilized by the investigative groups. On the other hand, there remains both confusion and indecision as to the influence HbCO has on other cardiovascular parameters.

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